EXHIBIT B

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 4 Cases*	

EXPERT REPORT OF OLGA RAMM, M.D.

Expert Report of Olga Ramm, M.D.

I. Qualifications

I am a Board Certified Female Pelvic Medicine and Reconstructive Surgery (FPMRS) subspecialist with my background in Obstetrics and Gynecology. I serve as the The Permanente Medical Group Northern California Regional Chief of Division Chiefs of FPMRS and am the Director of the Kaiser East Bay - UCSF FPMRS Fellowship Program. I am licensed to practice medicine in California. I treat patients with a wide range of isolated and complex pelvic floor disorders and, most commonly, patients with pelvic organ prolapse and urinary incontinence.

I graduated from the University of Kansas with a Bachelor of Science in Molecular Genetics and a Bachelor of Arts in Spanish Literature. I attended the University of Kansas School of Medicine and completed my Obstetrics & Gynecology residency at Northwestern University Feinberg School of Medicine in Chicago, where I served as chief administrative resident. I then completed a fellowship in Urogynecology - Female Pelvic Medicine and Reconstructive Surgery at Loyola University Medical Center in Chicago. My training and expertise include abdominal, laparoscopic, robotic, and vaginal FPMRS surgeries, including procedures for the treatment of pelvic organ prolapse and stress urinary incontinence. I have published peer reviewed journal articles and have presented at FPMRS and gynecologic surgery specialty conferences on urogynecologic conditions.

Over my career and currently, the TVT mid-urethral sling has been my preferred treatment for the surgical correction of stress urinary incontinence. I have performed approximately 1,400 surgeries utilizing Ethicon's original TVT Retropubic device. I was involved in 500 TVT cases in residency, 750 TVT cases in fellowship, and I have done approximately 600 TVT cases in my California practice. I have also utilized the TVT

Exact device and have observed no difference in its efficacy or safety.

I was first trained to perform the TVT retropubic sling during medical school. I was further trained on and began performing the TVT during my residency and fellowship, as is usual for urogynecologists, as competence in performing mid-urethral sling procedures for stress urinary incontinence is a requisite for the credentialing of FPMRS training programs in the United States. Likewise, knowledge of the indications for, safety, and efficacy of mid-urethral slings is also a part of the OB/Gyn and FPMRS Board Certification processes. In my surgical practice at Kaiser Permanente, I have exclusively used the TVT and TVT Exact mid-urethral slings. In my training, I have also been trained on and used the Ethicon TVT-O device for the surgical treatment of stress urinary incontinence, as it is also a standard of care in the field.

In my role as the Director of the FPMRS Fellowship Training Program and Chief of FPMRS at Kaiser Permanente Northern California, I am knowledgeable about the required training curriculum for FPMRS in residency and fellowship. I have given trainees didactic lectures to educate them about the indications, relative contraindications, expected outcomes, safety, and efficacy of the surgical and non-surgical treatment options for stress urinary incontinence. I have taught trainees to perform the TVT procedure in the operating room, as mid-urethral slings are recognized as the gold standard and first line approach in the surgical treatment of stress urinary incontinence by the American College of Obstetrics and Gynecology (ACOG) and the Accreditation Council for Graduate Medical Education (ACGME). I have received several honors and awards for didactic and surgical teaching, including The Council on Resident Education in Obstetrics and Gynecology (CREOG) National Faculty Award.

I have been trained on and have utilized other manufacturers' retropubic and transobturator mid-urethral sling devices. I also have training in and have performed, in

limited numbers, open, laparoscopic and robotic Burch urethropexy procedures and autologous pubovaginal slings. Notably, at the time of my residency and fellowship training, the data which was obtained in surgical trials using the TVT device overwhelmingly supported the use of mid-urethral slings as the first-line approach to uncomplicated stress urinary incontinence over these more invasive procedures that have higher morbidity and complication rates, longer recovery, and lower efficacy. In my practice, I am the receiving referral surgeon in Kaiser Permanente Northern California region for laparoscopic Burch procedures due to my extensive laparoscopic skills; I have continued to perform Burch procedures when they are indicated or when the patient declines a synthetic mid-urethral sling.

In summary, the TVT is my preferred procedure and constitutes over 95% of my stress urinary incontinence surgeries. I prefer the retropubic approach due to comfort with the device and the fact that it is supported by the largest multi-faceted body of high level evidence relative to any other surgical treatment option for stress urinary incontinence. The TVT's design, ease of use, minimally invasive approach, low morbidity and rapid patient recovery, and its immediate, short- and long-term durability, efficacy, and safety as further discussed make it the gold standard for the surgical treatment of stress urinary incontinence.

I have also been trained on and have performed native tissue and abdominal, laparoscopic and vaginal graft-reinforced pelvic organ prolapse surgery. I have experience in performing sacral colpopexy with Prolene mesh, Gynemesh PS and other meshes.

For further information regarding my education, training, experience and qualifications, my CV is enclosed as Attachment A.

II. Fees for Expert Work and Prior Expert Testimony

My hourly rate for expert work is $500 per hour and my rate for testimony is $600 per hour. I have not given expert testimony.

III. Materials Reviewed and Exhibits to be Used at Trial

In the preparation of this report, I have searched and reviewed the medical and scientific literature concerning the TVT device while considering the level of evidence in the practice of evidence-based medicine and formulation of evidence-based opinions. I have also reviewed documents from Ethicon as well as the Ethicon TVT Instructions for Use, TVT Surgeons Resource Monograph, and the Professional Education materials made available to pelvic surgeons as they are the users of the TVT device. I have also reviewed the Plaintiffs' expert reports and the materials cited by Plaintiffs' experts in their reports. A list of these materials and those that I may use at trial are attached to this report as Attachment B.

IV. Urinary Incontinence

Urinary incontinence is the involuntary leakage of urine. It is a very common condition among women, with 16% of women reporting incontinence symptoms during their lifetime and 30-50% reporting incontinence symptoms after age 60 [Sandvik H. Bergen, Norway: Department of Public Health and Primary Health Care, University of Bergen; 1995. Female urinary incontinence: studies of epidemiology and management in general practice]. Urinary incontinence has a profound influence on a woman's physical, emotional, and social well-being and has been implicated as an important independent risk factor for institutionalization and loss of independent functioning in elderly patients [Nuotio M, Tammela TL, Luukkaala T, Jylha M. (2003). Predictors of institutionalization in an older population during a 13-year period: The effect of urge incontinence. Journals of Gerontology Series A: Biological Sciences and Medical Science, 58, 756-762]. Additionally, urinary incontinence causes feelings of shame,

embarrassment, relationship stress, and social isolation [Fultz et al. Am J Obstet Gynecol 2003; Melville JL, Delaney K, Newton K, Katon W. Incontinence severity and major depression in incontinent women. Obstet Gynecol. 2005;106(3):585-592]. In addition to its psychoemotional impacts, urinary incontinence is responsible for tremendous cost to the healthcare system, with direct costs for women alone estimated at $12.4 billion in 1995 dollars [Wilson et al. Obstet Gynecol 2001; Nygaard I, Barber MD, Burgio KL, Kenton K, Meikle S, Schaffer J, Spino C, Whitehead WE, Wu J, Brody DJ; Pelvic Floor Disorders Network. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008 Sep 17;300(11):1311-16]. The number of women affected by urinary incontinence is projected to increase 55% by 2050 as the population continues to age, further driving up the economic burden of incontinence on the healthcare system [Wu et al, Obstet Gynecol 2009].

The IUGA/ICS 2010 Joint Report on the Terminology for Female Pelvic Floor Dysfunction outlines eight distinct types of urinary incontinence. In women with urinary incontinence, the most prevalent incontinence type is mixed incontinence, characterized by the complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing. Stress incontinence is the second most common type and the most common isolated type of urinary incontinence. Roughly 49% of women with urinary incontinence suffer from stress incontinence, which is characterized by the involuntary loss of urine associated with exertion that results in increased intraabdominal pressure, such as coughing, laughing, jumping, in the absence of the urge to urinate [Hampel et al, Urol 1997]. Multiple factors contribute to the development of stress incontinence, most notably injury to pelvic nerves, muscles and connective tissue, which is modulated by genetics and lifestyle choices, such as obesity or smoking [Rortveit G, Subak LL, Thom DH, Creasman JM, Vittinghoff E, Van Den Eeden SK, Brown JS. Urinary incontinence, fecal incontinence and pelvic organ prolapse in a population-based, racially diverse cohort: prevalence and risk factors. Female Pelvic Med Reconstr Surg. 2010 Sep;16(5):278-83]. Urgency incontinence, the

third most common urinary incontinence type, is characterized by involuntary leakage of urine following a sudden or severe urge to urinate.

Urinary continence is predicated upon the normal function and anatomy of several pelvic structures. The pudendal nerve and pelvic splanchnic nerves, which innervate the urethral continence mechanism, must have functional afferent and efferent pathways [Kenton K, FitzGerald MP, Shott S, Brubaker L. Role of urethral electromyography in predicting outcome of Burch retropubic urethropexy. Am J Obstet Gynecol. 2001 Jul;185(1): 51-5]. The urethral sphincter muscles and their attachments must be intact [Fleischmann N, Flisser AJ Blaivas JG, Panagopoulos G. Sphincteric urinary incontinence: relationship of vesical leak point pressure, urethral mobility and severity of incontinence. J Urol. 2003 Mar;169(3)999-1002; DeLancey JO, Trowbridge ER, Miller JM, Morgan DM, Guire K, Fenner DE, Weadock WJ, Ashton-Miller JA. Stress urinary incontinence: relative importance of urethral support and urethral closure pressure. J Urol. 2008 Jun;179(6):2286-90]. Vascular supply and the thickness and turgor of the periurethral tissues must allow for coaptation of the urethral mucosa [Ashton-Miller JA, DeLancey JO. Functional anatomy of the female pelvic floor. Ann N Y Acad Sci. 2007 Apr;1101:266-96]. The effects of childbirth, aging, prior surgery, and medical comorbidities can negatively affect the function of these pelvic structures, causing stress urinary incontinence.

Urinary incontinence frequently presents concurrently with other pelvic floor disorders in the same patient. Some, such as pelvic organ prolapse, fecal incontinence, and defecatory dysfunction, share a common pathophysiology, with impaired function of nerve, muscle, and connective tissues. Urinary incontinence is also known to be significantly associated with sexual dysfunction, conferring an odds ratio of 1.96 for low libido, OR 2.11 for vaginal dryness, and OR 2.04 for dyspareunia [Handa et al. Am J Obstet Gynecol 2004; Aslan G et al. Int J Impot Res. 2005].

The diagnosis of stress urinary incontinence can most commonly be made clinically. Women presenting with stress incontinence complain of involuntary loss of urine on effort or physical exertion (e.g., sporting activities), or on sneezing or coughing. A positive office cough stress test is a reliable sign of stress urinary incontinence and, together with bothersome symptoms in the absence of an elevated postvoid residual or other urinary tract abnormalities, is an indication for surgical treatment of pure stress incontinence in women with adequate (Stage 2 or less) pelvic organ support [Nager CW et al. A randomized trial of urodynamic testing before stress-incontinence surgery. N Engl J Med. 2012 May 24;366(21):1987-97]. Female pelvic floor specialists will often evaluate women with symptoms of urgency incontinence or symptomatic prolapse with preoperative simple cystometry or multichannel urodynamic testing. Many female pelvic reconstructive surgeons utilize validated symptom-specific questionnaires, such as the Pelvic Floor Distress Inventory, the Pelvic Floor Impact Questionnaire, the International Consultation on Incontinence Questionnaire, or the Medical Epidemiology and Social Aspects of Aging Questionnaire [Barber MD et al. AJOG 2005; Avery K et al. *Neurourol Urodynamics* 2001;20:510-1, MESA ref] to track patient-reported outcomes objectively.

V. Non-Surgical Management of Stress Urinary Incontinence

Once the diagnosis of stress urinary incontinence has been made, female pelvic floor specialists will discuss treatment options in the context of the individual patient's goals, functional status, medical comorbidities, reproductive plans, and surgical history. Patient satisfaction with treatment is correlated with the achievement of patient selected goals [Elkadry EA, Kenton KS, FitzGerald MP, Shott S, Brubaker L. Patient-selected goals: a new perspective on surgical outcome. Am J Obstet Gynecol. 2003 Dec;189(6):1551-7]. Some patients may choose to avoid surgery or to reserve surgical treatment as a last resort in the treatment algorithm of stress incontinence. Proposed quality measures of urinary incontinence treatment have suggested that all patients should be counseled about the typical treatment course and expected outcomes of

pelvic floor muscle training and pessary, and that patients should be offered these conservative treatments in addition to surgery [Anger JT et al. Neurourol Urodyn. 2013 Nov;32(8):1058-63].

VI. Prior Surgeries Necessitated the Design and Development of TVT for the Surgical Management of Stress Urinary Incontinence

The introduction of the TVT mid-urethral sling by Ulmsten and Petros in the 1990s revolutionized surgical treatment of stress urinary incontinence by making it more accessible to women due to its minimally invasive approach, high efficacy, rapid recovery, and low complication rate [Ulmsten U and Petros P, Scand J Urol Nephrol. 1995 Mar;29(1):75-82].

Prior to synthetic mid-urethral slings, surgical treatment of stress incontinence was focused on bladder neck elevation or fixation. The autologous fascial sling, first described by Goebell and Stoeckel in 1910 [Aldridge AH. Transplantation of fascia for relief of urinary stress incontinence. Am J Obstet Gyncol 1942;44: 398-411] and later popularized by Maguire [J Urol. 2002 Feb;167(2 Pt 2):1120-3; Pubovaginal sling procedure for stress incontinence. 1978. McGuire EJ, Lytton B.], involved harvesting a rectangular strip of rectus fascia, then positioning it under the bladder neck by passing it retropubically and attaching each end abdominally with suspensory sutures to the rectus fascia away from the harvesting incision [Walters MD, Karram MM, eds. Urogynecology and Reconstructive Surgery, ed 4. Philadelphia: Saunders; 2015].

The pubovaginal sling resulted in suspending the bladder neck, thus creating enough tension to occlude the bladder neck with increased intra-abdominal pressure. The procedure's efficacy, 66% based on a composite measure of success, is tempered by its morbidity [Albo ME, Richter HE, Brubaker L, Norton P, Kraus SR, Zimmern PE, Chai TC, Zyczynski H, Diokno AC, Tennstedt S, Nager C, Lloyd LK, FitzGerald M, Lemack

GE, Johnson HW, Leng W, Mallett V, Stoddard AM, Menefee S, Varner RE, Kenton K, Moalli P, Sirls L, Dandreo KJ, Kusek JW, Nyberg LM, Steers W; Urinary Incontinence Treatment Network.. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med. 2007 May 24;356(21):2143-55]. The fascial harvest required by this procedure necessitates an abdominal incision with its associated complications. In one of the few studies describing complications from native tissue harvest, Walter et al reported rates of immediate postoperative complications in women: 1% hematoma requiring drainage, 3% seroma, and 7% wound infection or cellulitis requiring oral antibiotic treatment. Moreover, the rate of patient dissatisfaction at 2 years after surgery was 13%, for reasons that included unacceptable cosmetic outcome, discomfort at the harvest site, or both [Walter AJ, Hentz JG, Magrina JF, Cornella JL. Harvesting autologous fascia lata for pelvic reconstructive surgery: Techniques and morbidity. Am J Obstet Gynecol. 2001 Dec;185(6):1354-8]. Moreover, the fascial sling conferred a relatively high rate of voiding dysfunction (14%) that necessitated subsequent sling release (6%) [Albo et al. NEJM 2007]. Interestingly, there are reports and case series describing vaginal erosion of autologous fascial slings at a rate of 0.8%, despite the sling's native tissue origins [Athanasopoulos A, Gyftopoulos K, McGuire EJ. Efficacy and Preoperative Prognostic Factors of Autologous Fascia Rectus Sling for Treatment of Female Stress Urinary Incontinence. Urology. 2011 Nov;78(5):1034-8a].

The Marshall-Marchetti-Kranz (MMK) procedure, described by Victor Marshall, Andrew Marchetti and Kermit Kranz in 1949, relied upon elevating and fixing the bladder neck to the pubic symphysis. This procedure, most commonly performed through a Pfannenstiel incision, was associated with the pain, recovery, and complications of an open abdominal surgery, as well as voiding dysfunction and osteitis pubis [Quadri G et al. AJOG 1999; Kammerer-Doak DN, Cornella JL, Magrina JF, Stanhope CR, Smilack J. Osteitis pubis after Marshall–Marchetti–Krantz urethropexy: a pubic osteomyelitis. Am J Obstet Gynecol 1998;179:586–90]. Over a decade later, John Burch modified the retropubic urethropexy by using Cooper's ligaments as the fixation point for the

periurethral tissue [Burch J. Cooper's Ligament Urethrovesical Suspension for Stress Incontinence. Am J Obstet Gynecol 1968;100:764-74]. Surgical outcomes and perioperative complications for both open and laparoscopic approaches to the Burch urethropexy have been described, citing a 22% rate of voiding dysfunction, 13% rate of de novo development of uterovaginal prolapse, and an increase in postoperative dyspareunia [Chaliha C, Stanton SL. Complications of surgery for genuine stress incontinence. Br J Obstet Gynaecol. 1999 Dec;106(12):1238-45]. Published rates of dyspareunia have ranged from 3% to 19%, with Weber et al finding the Burch urethropexy and posterior colporrhaphy to be independent predictors of postoperative dyspareunia when performed in conjunction with native tissue apical suspension for prolapse repair [Demirci F, Yucel O, Eren S, Alkan A, Demirci E, Yildirim U. Long-term results of Burch colposuspension. Gynecol Obstet Invest. 2001;51(4):243-7; Weber AM, Walters MD, Piedmonte MR. Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol. 2000 Jun;182(6):1610-5].

It is important to consider these complications in the context of the Burch procedure's limited efficacy in the treatment of stress incontinence, determined to be 49%-51% in randomized surgical trials [Albo et al. NEJM 2007; Ward KL et al. Am J Obstet Gynecol 2004]. Moreover, there is a significant decline in intermediate and long-term success rates with open and laparoscopic colposuspension [Demirci F, Yucel O, Eren S, Alkan A, Demirci E, Yildirim U. Long-term results of Burch colposuspension. Gynecol Obstet Invest. 2001;51(4):243-7; Kjølhede P . Long-term efficacy of Burch colposuspension: a 14-year follow-up study. Acta Obstet Gynecol Scand 2005;84:767-72; Barr S, Reid FM, North CE, Hosker G, Smith AR. The long-term outcome of laparoscopic colposuspension: a 10-year cohort study. Int Urogynecol J 2009;20:443-5; Alcalay M, Monga A, Stanton SL. Burch colposuspension: a 10-20 year follow-up. BJOG 1995;102:740-5].

VII. Historical Use of Mesh for SUI

The limitations and morbidity associated with autologous tissue harvest, as described above, have motivated pelvic surgeons to seek synthetic materials that could be safely applied toward more efficacious surgical treatment of stress urinary incontinence. The limitations of each material and the evolution of mesh materials, guided by increased understanding of the biological interface between native tissue and synthetic implants, fueled experimentation with various mesh materials prior to widespread adoption of type I polypropylene mesh as the material of choice.

In 1962 Williams and TeLinde described the use of nylon and Mersilene mesh for a suburethral sling used for correction of stress urinary incontinence [Williams TJ, TeLinde RW. The sling operation for urinary incontinence using mersilene ribbon. Obstet Gynecol. 1962 Feb;19:241-5]. In 1968, Moir published his case series of 71 patients who had undergone the "Gauze-Hammock operation", which involved placement of a 2.5 cm wide Mersilene mesh sling suburethrally [Moir JC. The gauze-hammock operation. (A modified Aldridge sling procedure). J Obstet Gynaecol Br Commonw. 1968 Jan;75(1):1-9]. In 1970, Morgan presented his experience with the use of polypropylene (Marlex) mesh sling that was fixed to Cooper's ligaments for treating recurrent stress urinary incontinence in patients with pelvic scar tissue [Morgan JE. A sling operation, using Marlex polypropylene mesh, for treatment of recurrent stress incontinence. Am J Obstet Gynecol. 1970 Feb 1;106(3):369-77]. In 1983, Fianu described the use of absorbable material, Vicryl, for constructing a stress urinary incontinence sling [Fianu S, Söderberg G. Absorbable polyglactin mesh for retropubic sling operations in female urinary stress incontinence. Gynecol Obstet Invest. 1983;16(1):45-50]. In 1985, Stanton et al. described the use of a Silastic (Dacron/Silicone) sling for stress urinary incontinence and in 1988, Horbach et al. published on the use of a Gore-Tex sling [Stanton SL, Brindley GS, Holmes DM. Silastic sling for urethral sphincter incompetence in women. Br J Obstet Gynaecol. 1985 Jul;92(7):747-50, Horbach NS, Blanco JS, Ostergard DR, Bent AE, Cornella JL. A

suburethral sling procedure with Polytetrafluoroethylene for the treatment of genuine stress incontinence in patients with low urethral closure pressure. Obstet Gynecol. 1988]. Petros' initial prototype for the TVT sling involved the use of Mersilene mesh, which was later abandoned in favor of polypropylene mesh due to its superior tolerability and lower complication rate [Petros. Int Urogynecol J. 2014]. The use of various synthetic materials and their efficacy and complication profile in the treatment of pelvic organ prolapse and stress urinary incontinence was reviewed by Iglesia et al in 1997 [Iglesia CB, Fenner DE, Brubaker L. The use of mesh in gynecologic surgery. Int Urogynecol J. 1997;8(2):105-15].

VIII. Development of the TVT

The integral theory of female urinary incontinence, published by Ulmsten and Petros in 1990, was predicated upon the role of urethral support and stabilization by pubourethral ligaments in maintaining urinary continence [Petros PE and Ulmsten UI. Acta Obstet Gynecol Scand. 1990]. Rather than focusing on elevation or fixation of the bladder neck, Ulmsten and Petros focused on stabilizing the mid-urethra in stress incontinent women with a neoligament fashioned out of collagen ingrowth into a mesh sling implant [Petros P and Ulmsten U. Intravaginal slingplasty. An ambulatory surgical procedure for treatment of female urinary incontinence. Scand J Urol Nephrol 1995;29:75-82]. After testing the procedure's safety in a large mammalian model, the dog, the procedure was initially attempted in stress incontinent women using a removable mesh implant; however the recurrence rate after removal of the temporary implant was upwards of 50%, prompting a shift towards permanent sling implants [Petros P and Ulmsten U. An integral theory on female urinary incontinence. Experimental and Clinical considerations. Acta Obstet Gynecol Scand. 1990;69(suppl):153]. In developing what is now the TVT, various materials, such as Gore-tex, Mersilene, Teflon, and Marlex, were tried and found to have unacceptably high (up to 10%) rejection rates. In 1996, Ulmsten et al published on the results of a modified intravaginal slingplasty, the TVT device manufactured by Johnson and Johnson, comprised of a metal handle with a curved

introducer 5mm in diameter, attached to a 10mm wide prolene sling covered by a plastic sheath, which prevented the contamination of the sling prior to insertion while allowing the ends of the sling to be pulled up and adjusted without trauma [Ulmsten et al. Int Urogynecol J. 1996]. In 2001, Falconer and Ulmsten published the results of their comparison of collagen metabolism from periurethral biopsies taken in women treated with mersilene and prolene mid-urethral slings [Falconer C et al. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogyncol J. 2001 (suppl 2): S19-23]. Their findings were notable for highly enhanced paraurethral collagen extractability, marked inflammation, and fibrosis around the implant in the mersilene group and no change in collagen extractability or concentration in the prolene group, as compared to the control group comprised of continent women undergoing gynecologic surgery for menorrhagia. These results were clinically reflected by a 20% sling erosion rate in the mersilene group and no erosions in the prolene group.

IX. Clinical Data on the Performance of the TVT

Since its introduction in 1998, the TVT mid-urethral sling has gained widespread acceptability, with its efficacy, safety, complication profile, and durability extensively described in the literature and compared with other anti-incontinence operations. In 1995, Nilsson et al carried out a multi-centered prospective surgical trial of TVT procedures for primary treatment of stress incontinence in a cohort of Scandinavian women and reported an 85% cure rate and 10.6% significant improvement rate at 5 years postoperatively [Nilsson et al. Int Urogynecol J. 2001]. Large case series, such as the one published by Agostini et al, described the intraoperative safety of TVT based on a cohort of 12,280 TVT procedures, noting a 7% rate of intraoperative cystotomy, 6.5% rate of postoperative retention requiring prolonged catheterization, 0.2% risk of vaginal mesh extrusion, 0.3% risk of hematoma, and 0.08% rate of major organ injury [Agostini A. et al. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2006].

By 2002, the TVT was the procedure of choice (49%) for the treatment of female stress incontinence among members of the International Urogynecologic Association, followed closely by the Burch procedure (44%) [Davila GW et al. Int Urogynecol J. 2002].

In 2002, Karen Ward and Paul Hilton published their prospective randomized trial comparing TVT and Burch for primary treatment of stress incontinence [Ward K et al. BMJ. 2002]. Short- and longer-term results were comparable based on a composite outcome of negative stress test on urodynamic testing and a negative 1 hour pad test (73% vs 64% cure rate at 6 months and 63% vs 51% cure rate at 2 years for the TVT and Burch groups, respectively). Not surprisingly, given the minimally invasive nature of the TVT, study participants in the TVT group reported significantly higher scores in emotional, social, and physical function and vitality health dimensions tested by a validated questionnaire. The TVT group also had significantly lower intraoperative blood loss, postoperative opiate use, need for indwelling foley postoperatively, and incidence of fever and a shorter duration of hospital stay with a more rapid recovery to work. There were no significant differences in the rates of dyspareunia, painful vaginal dryness, urinary hesitancy, intermittency, straining, an abnormal urinary stream, or urgency and urge incontinence. In 2004, Paraiso et al published the results of their randomized trial comparing TVT to laparoscopic Burch, noting a significantly longer intraoperative time in the Burch group (210 minutes vs 141 in the TVT group) and substantially lower efficacy based on multichannel urodynamic study results at 1 year after surgery (18.8% rate of urodynamic stress incontinence in the Burch group, compared to 3.2% in the TVT group) [Paraiso et al. Obstet Gynecol. 2004].

By 2005, the TVT mid-urethral sling was regarded as the standard first-line approach to the treatment of stress urinary incontinence and served as a reference for comparison with any newer procedures or devices [2005 ACOG Practice Bulletin #63]. In 2004, Tseng et al published the results of their randomized comparison of the suprapubic arc sling (SPARC) and the TVT, noting similar cure rates for SPARC (80.7%) and TVT

(87.1%), but a higher bladder injury rate with SPARC (13% vs 0% in TVT group) [Tseng et al. Int Urogynecol J. 2005]. In 2001, Delorme described the transobturator approach to mid-urethral sling placement using an “outside-in” technique [Delorme E. Prog Urol. 2001]. Unfortunately, the Uratape mesh, a multifilament microporous mesh with pores <10 microns initially used for this procedure, was associated with high rates of vaginal erosion and was withdrawn from the market and replaced with Obtape, a monofilament polypropylene mesh with pore size of 50 microns [Siegel AL. Urology 2005]. De Leval modified the transobturator approach to an “inside-out” technique using the same monofilament macroporous (>75 micron pore size) mesh used with the TVT [de Leval J. Eur Urol. 2003]. In 2006, Abdel-Fattah et al published a comparison of the Obtape sling and TVT-O sling, noting a substantially higher (7.3% vs 1.8%) rate of sling extrusion into the vagina in the Obtape group and establishing the clinical superiority of macroporous mesh design [Abdel-Fattah M et al. BJU. 2006].

The long-term safety and efficacy of the TVT procedure were borne out by long-term follow-up studies, such as Nilsson’s 17 year follow-up in a cohort of 90 women who underwent TVT [Nilsson et al. Int Urogynecol J. 2013]. Of the 46 women available for objective follow up, 42 (91%) were objectively cured, as defined by a negative stress test and 87.2% considered themselves subjectively cured based on validated questionnaires. Similarly, Olsson reported on a cohort of 124 women (104 were examined and an additional 20 patients with telephone consultation) with 11 and a half years follow up and found that 84% (87/104) were objectively cured, as defined by a negative cough stress test, 77% (95/124) were subjectively cured with an additional 18.5% (23/124) reporting improvement, and 94% were satisfied (74% very satisfied and 20% satisfied). [Olsson I, Abrahamsson AK, Kroon UB. Long-term efficacy of the tension-free vaginal tape procedure for the treatment of urinary incontinence: a retrospective follow-up 11.5 years post-operatively. Int Urogynecol J. 2010 Jun;21(6):679-83].

In a 10 year follow up study by Serati of 58 women, 52 were satisfied (90%) and 54 (93%) were at least improved, 54 women (93%) were objectively cured, and 53 (91%) had urodynamically confirmed cure [Serati M, Ghezzi F, Cattoni E, Braga A, Siesto G, Torella M, Cromi A, Vitobello D, Salvatore S. Tension-free vaginal tape for the treatment of urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up. Eur Urol. 2012 May;61(5):939-46]. At 13 years follow up in the same cohort but with 55 women available for follow up, 47 were satisfied (85.5%) and 48 (87%) were at least improved, 50 women (91%) were objectively cured, and 49 (89%) had urodynamically confirmed cure [Serati M, Sorice P, Bogani G, Braga A, Cantaluppi S, Uccella S, Caccia G, Salvatore S, Ghezzi F. TVT for the treatment of urodynamic stress incontinence: Efficacy and adverse effects at 13-year follow-up. Neurourol Urodyn. 2017 Jan;36(1):192-197]. Svenningsen reported on a cohort of 483 women (327 were examined and an additional 156 patients with telephone consultation) who underwent TVT and at 10 years follow up found that 90% were objectively cured, as defined by a negative stress test, 76% were subjectively cured, 94% were subjectively improved, and 83% were very satisfied [Svenningsen R, Staff AC, Schiøtz HA, Western K, Kulseng-Hanssen S. Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J. 2013 Aug;24(8):1271-8].

Significant research efforts have been focused on comparing the safety, efficacy, and complication profile of the retropubic and the transobturator approaches to midurethral sling placement. In 2009 Laurikainen et al published the 2 month results of a randomized trial of 267 women comparing the TVT to the TVT-O and detected no significant differences in objective or subjective cure rates [Laurikainen E et al. Retropubic compared with transobturator tape placement in treatment of urinary incontinence: a randomized controlled trial. Obstet Gynecol. 2007 Jan;109(1):4-11]. The five year outcomes, with 95% of patients available for follow-up, showed similar success rates in the two groups (94.2% in the TVT and 91.7% in the TVT-O group). These results were supported by the randomized trial comparing transobturator (TVT-O and

Monarc slings were utilized) and retropubic (TVT was the only retropubic sling utilized) published in 2010 by Richter et al [Richter HE et al. Retropubic versus transobturator midurethral slings for stress incontinence. NEJM 2010]. The primary outcome was treatment success at 12 months according to both objective criteria (a negative stress test, a negative pad test, and no retreatment) and subjective criteria (self-reported absence of symptoms, no leakage episodes recorded, and no retreatment). The rates of objectively assessed treatment success were equivalent (80.8% in the retropubic sling group and 77.7% in the transobturator-sling group). Subjectively assessed success rates favored the retropubic approach (62.2% in the retropubic versus 55.8% in the transobturator group), but did not meet the trial's 12% difference for non-equivalence. The rates of voiding dysfunction requiring surgery were 2.7% in those who received retropubic slings and 0% in those who received transobturator slings. There were no significant differences between groups in postoperative urge incontinence, satisfaction with the results of the procedure, or quality of life.

The large number of cohort studies and clinical randomized trials involving the TVT allowed for robust meta-analyses of outcomes following the TVT. In 2009, Ogah et al published a Cochrane review of minimally invasive synthetic slings for stress urinary incontinence, concluding that synthetic sling operations appeared to be as effective as open retropubic colposuspension in the short- and long-term with fewer perioperative complications, less postoperative voiding dysfunction, shorter operative time and hospital stay. The authors also reported that whereas some studies found laparoscopic Burch to be comparable in efficacy to the TVT, other studies concluded that synthetic midurethral slings had superior efficacy; however the synthetic suburethral sling operations had significantly less de novo urgency and urgency incontinence, shorter operating time, hospital stay and time to return to daily activities. A retropubic bottom-to-top route, employed by the TVT, was found to be more effective than the top-to-bottom route and incurred significantly less voiding dysfunction, bladder perforations and tape erosions. Monofilament tapes had significantly higher objective cure rates compared to

multifilament tapes and fewer tape erosions (1.3% versus 6%) [Ogah J et al. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006375].

In 2010, Novara et al published their analysis of 39 randomized trials and concluded that patients receiving midurethral tapes had significantly higher overall and objective cure rates than those receiving Burch colposuspension, although they had a higher risk of intraoperative bladder perforations. Patients undergoing midurethral synthetic slings and pubovaginal autologous slings had similar cure rates, although those treated with autologous sling were slightly more likely to experience urgency, voiding dysfunction, and had a higher reoperation rate [Novara G. et al. Eur Urol. 2010].

In 2014, the Systematic Review Group of the Society of Gynecologic Surgeons published their results of a meta-analysis of randomized trials of surgical repairs of stress incontinence that reported outcomes at a minimum of 12 months of follow-up. They reported no significant difference in efficacy between Burch and midurethral slings, increased efficacy of pubovaginal autologous sling as compared with Burch, and higher patient satisfaction in women treated with midurethral sling as compared to autologous pubovaginal sling [Schimpf et al. Am J Obstet Gynecol. 2014].

More recently, in 2015 Ford and Ogah updated their Cochrane review of midurethral slings, which included 12,113 women [Ford AA et al. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;(7):CD006375]. The authors included several large surgical registries of TVT procedures, ranging from 809 to 4,281 in size. These registries reflected the low complication rates reported in randomized clinical trials and other metaanalyses: bladder perforation rates of 2.7-3.9%, reoperation rates relating to tape insertion or postoperative voiding dysfunction of 1.6-2.4%, clinically significant urinary retention rate

of 1.6%, pelvic hematoma rate of 0.7-1.9%, a 0.7% infection rate, 1.5% sling extrusion rate, and 0.4% rate of groin pain. This review concluded that "mid-urethral sling operations have been the most extensively researched surgical treatment for stress urinary incontinence in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term. This review illustrates their positive impact on improving the quality of life of women with stress urinary incontinence".

X. Complications of TVT

Mesh extrusion

As previously noted in this report, many materials, biologic and synthetic, have been trialed in the search for the ideal graft material for a suburethral sling. The reference group, autologous slings fashioned from the patient's native fascial tissue, had a reported erosion rate of 0.8% [Athanasopoulos A, Gyftopoulos K, McGuire EJ. Efficacy and Preoperative Prognostic Factors of Autologous Fascia Rectus Sling for Treatment of Female Stress Urinary Incontinence. Urology. 2011 Nov;78(5):1034-8a]. Moreover, there are case reports of late complications due to intravesical sutures following Burch colposuspension despite intraoperative cystoscopy [Dwyer PL, Carey MP, Rosamilia A. Suture injury to the urinary tract in urethral suspension procedures for stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10:15–21]. Early synthetic graft materials had substantially higher erosion rates, up to 15% for Obtape, 10% for Gore-tex, Teflon, and Marlex and up to 6% for Mersilene [Dobson et al. Transobturator surgery for stress urinary incontinence: one year follow-up of a cohort of 52 women. Int Urogynecol J Pelvic Floor Dysfunct 2007. 18:27-32; Petros P and Ulmsten U. An integral theory on female urinary incontinence. Experimental and Clinical considerations. Acta Obstet Gynecol Scand. 1990;69(suppl):153]. Mesh complication rates were greatly reduced with the use of the Prolene polypropylene mesh. Long-term follow-up studies specific to the TVT device demonstrate a mesh extrusion rate of 0.9%

[Nilsson CG].

In 2011, Ogah et al published the Cochrane review of minimally invasive synthetic suburethral sling operations which included 62 RCTS involving 7,101 women and reported that monofilament tapes (and in particular TVT), in addition to having higher objective cure rates than multifilament tapes, had lower mesh erosion rates (1.3% vs 6%).

In their 2013 review of 188,454 mid-urethral sling procedures performed between 2001 and 2010, Jonsson Funk et al found that the 9 year risk of mesh erosion/extrusion was 2.5% [Jonsson Funk et al. Sling revision/removal for mesh erosion and urinary retention: long-term risk and predictors. Am J Obstet Gynecol. 2013 Jan;208(1):73.e1-7]. It is likely that in this nationwide database, midurethral slings from materials other than polypropylene were included in the earlier years of the study, thus elevating the mesh complication rate. Unger et al performed a case-control study of all women treated with midurethral sling for stress incontinence at the Cleveland Clinic Foundation who subsequently required a sling revision between 2003 and 2013 [Unger CA et al. Indications and risk factors for midurethral sling revision. Int Urogynecol J. 2016 Jan;27(1):117-122]. They found a 0.5% sling revision rate for mesh extrusion. This rate can be viewed in the context of foreign body complications due to mesh implants in other applications, such as abdominal wall hernia repair, where mesh-related complications are described at rates of 1-10% [Brown RH, Subramanian A, Hwang CS, et al. Comparison of infectious complications with synthetic mesh in ventral hernia repair. Am J Surg 2013;205:182–7]. These rates illustrate the comparative safety and low complication rate of the TVT sling.

Voiding dysfunction

Urinary retention, voiding dysfunction and irritative voiding symptoms have all been

described following surgery for stress urinary incontinence. A large case control study recently described a 22% failure rate of the initial voiding trial on day of surgery, followed by rapid resolution of urinary retention in the first postoperative week in 98.5% of patients [Ripperda CM et al. Predictors of early postoperative voiding dysfunction and other complications following a midurethral sling. Am J Obstet Gynecol. 2016 Nov;215(5):656]. The 2-5% rate of long-term voiding dysfunction has been consistent across large case series [Glavind K, et al. Incidence and treatment of postoperative voiding dysfunction after the tension-free vaginal tape procedure. Int Urogynecol J. 2015 Nov;26(11):1657-60], randomized controlled trials [Brubaker L et al. Adverse events over two years after retropubic or transobturator midurethral sling surgery. AJOG 2011;] and meta-analyses [Ford AA et al. Cochrane Database Syst Rev. 2015 Jul 1;(7):CD006375]. Thus, postoperative urinary retention and voiding dysfunction are well-known and carefully characterized complications of mid-urethral sling surgery and anti-incontinence surgery in general. As described in this report, autologous fascial slings result in a 14% rate of voiding dysfunction [Albo et al. NEJM 2007]. One of the largest randomized trials comparing TVT with Burch urethropexy reports a 6% rate of prolonged catheterization in the TVT group compared with a 21% rate in the Burch group [Ward K et al. Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ 2002]. The informed consent process for any anti-incontinence procedure includes the disclosure of the risk of urinary retention and postoperative voiding dysfunction and a thorough discussion of subsequent management.

UTIs

Urinary tract infections are very common and affect women at a much higher incidence than men [Foxman B. Brown P. Epidemiology of urinary tract infections: transmission and risk factors, incidence, and costs. Infect Dis Clin North Am 2003; 17(2):227-41]. Urinary incontinence also appears to be associated with bacteriuria. One large study of elderly community-dwelling Swedish women found that those with urinary incontinence

had an odds ratio of 2.83 of having bacteriuria as compared to continent women [Rodhe N, Englund L, Molstad S, Samuelsson E. Bacteriuria is associated with urge incontinence in older women. Scand J Prim Health Care. 2008;26(1):35-9].

Recurrent urinary tract infections are also common in women. Haylen et al reported on a cohort of 1,140 women presenting for initial urogynecological assessment and found that 27% had 1 or more symptomatic and medically confirmed UTIs in the prior 12 month period and there was a 19% rate of recurrent UTI. [Haylen BT, Lee J, Husselbee S, Law M, Zhou J. Recurrent urinary tract infections in women with symptoms of pelvic floor dysfunction. Int Urogynecol J Pelvic Floor Dysfunct. 2009;20(7):837-42]. Similar rates were reported in a study that assessed recurrent UTI, diagnosed by two or more positive urine cultures taken within 12 months of each other, in women with prolapse (case) as compared to women with other gynecologic conditions (controls), with recurrent urinary tract infection seen in 21% of cases versus 18% in the control group (p=0.316) [Töz E, Kurt S, Sahin Ç, Canda MT. Frequency of recurrent urinary tract infection in patients with pelvic organ prolapse. Res Rep Urol. 2015 Jan 28;7:9-12].

Urethral and bladder instrumentation that are a part of the preoperative evaluation and intraoperative procedures for the treatment of stress incontinence further increase the risk of developing a urinary tract infection. It is, therefore, not surprising that UTIs are the most frequent complication of anti-incontinence surgery, affecting 13-32% of women [Ward K et al. BMJ 2002; Brubaker et al. AJOG 2011]. In fact, urinary tract infections are common complication of general gynecologic surgery, with 2.5% rates of postoperative UTI reported following hysterectomy alone [Gehrich AP, Lustik MB, Mehr AA, Patzwald JR. Risk of postoperative urinary tract infections following midurethral sling operations in women undergoing hysterectomy. Int Urogynecol J. 2016 Mar;27(3):483-90]. In a large multicenter, randomized surgical trial, the Stress Incontinence Surgical Treatment Efficacy Trial (SISTER) that compared the efficacy and safety of the autologous sling and Burch procedures, at 24 months follow up urinary

tract infection was noted to have occurred in 157 women in the autologous sling group (48%, with 305 UTI events) and 105 women in the Burch group (32%, with 203 UTI events) [Albo ME, Richter HE, Brubaker L, Norton P, Kraus SR, Zimmern PE, Chai TC, Zyczynski H, Diokno AC, Tennstedt S, Nager C, Lloyd LK, FitzGerald M, Lemack GE, Johnson HW, Leng W, Mallett V, Stoddard AM, Menefee S, Varner RE, Kenton K, Moalli P, Sirls L, Dandreo KJ, Kusek JW, Nyberg LM, Steers W; Urinary Incontinence Treatment Network.. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med. 2007 May 24;356(21):2143-55].

The published rates of postoperative UTI vary based on inclusion criteria for diagnosis of infection and range from 3.4% to 13% [Gehrich et al. Int Urogynecol J 2016; Brubaker et al. AJOG 2011]. The report on 2 year complications seen in a randomized trial following mid-urethral sling describes a 7% rate of recurrent urinary tract infection [Brubaker et al. AJOG 2011]. The bacterial pathogenicity and antibiotic susceptibility profile of hospital-acquired postoperative UTI contributes to the recurrent nature of the infections [Hisano M, Bruschini H, Nicodemo AC, Gomes CM, Lucon M, Srougi M. The Bacterial Spectrum and Antimicrobial Susceptibility in Female Recurrent Urinary Tract Infection: How Different They Are From Sporadic Single Episodes? Urology. 2015 Sep;86(3):492-7]. Women with new onset recurrent urinary tract infections following anti-incontinence surgery must have an evaluation of their lower urinary tract to exclude the possibility of an intravesical foreign body, such as suture in the case of urethropexy and native tissue pubovaginal sling or mesh in the case of mid-urethral sling, serving as a nidus for infection. There is a low (0.3%) but present rate of mesh erosion into bladder or urethra following TVT and pelvic reconstructive surgeons must counsel patients about this risk prior to surgery.

Dyspareunia

Sexual dysfunction and dyspareunia are very common conditions among women, with

some reports quoting a prevalence as high as 20-40% [Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors [published correction appears in JAMA. 1999;281(13):1174; Jamieson DJ, Steege JF. The prevalence of dysmenorrhea, dyspareunia, pelvic pain, and irritable bowel syndrome in primary care practices. Obstet Gynecol. 1996;87(1):55-8]. Pelvic floor disorders, including urinary incontinence, are associated with an even higher prevalence of sexual dysfunction, with incontinent women more likely to report less sexual desire, decreased sexual comfort and lower sexual satisfaction than their continent counterparts despite having a similar frequency of sexual activity [Felippe MR, Zambon JP, Girotti ME, Burti JS, Hacad CR, Cadamuro L, Almeida F. What is the real impact of Urinary Incontinence on Female Sexual Dysfunction? Sex Med. 2017 Jan 10.S 2050-1161]. Incontinent women are also more likely to report abstinence than continent controls. In a study of sexually active women planning hysterectomy for benign indications, severe urinary incontinence was significantly associated with decreased libido, vaginal dryness, and dyspareunia, even after adjusting for age [Handa VL, Harvey L, Cundiff GW, Siddique SA, Kjerulff KH. Sexual function among women with urinary incontinence and pelvic organ prolapse. Am J Obstet Gynecol. 2004 Sep; 191(3):751-6]. Treatment of urinary incontinence can improve sexual function in older women. In a 2006 study done among sexually active women who underwent midurethral slings procedures for the correction of urinary incontinence, increased coital frequency, decrease fear of incontinence with coitus, decreased embarrassment due to incontinence was reported six months after surgery [Ghezzi F, Serati M, Cromi A, Uccella S, Triacca P, Bolis P. Impact of tension-free vaginal tape on sexual function: results of a prospective study. Int Urogynecol J Pelvic Floor Dysfunct. 2006 Jan; 17(1):54-9.]. Studies that have used disease non-specific validated questionnaires, such as the FSFI, to measure sexual function following surgical treatment of stress incontinence have not been demonstrated to change libido, arousal, lubrication, orgasm, and sexual satisfaction [Pauls RN, Silva WA, Rooney CM, Siddighi S, Kleeman SD, Dryfhout V, Karram MM. Sexual function after vaginal surgery for pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol. 2007 Dec; 197(6):622.e1-7]. No change in the prevalence of dyspareunia or

ability to reach orgasm was noted before and after the midurethral sling procedure [Ghezzi F, Serati M, Cromi A, Uccella S, Triacca P, Bolis P. Impact of tension-free vaginal tape on sexual function: results of a prospective study. Int Urogynecol J Pelvic Floor Dysfunct. 2006 Jan; 17(1):54-9]. The risk of pain, dyspareunia and sexual dysfunction in patients treated with TVT is also lower than that of non-mesh incontinence surgeries as shown by numerous level 1 studies and large series following patients for at least a decade [Schimpf et al. Am J Obstet Gynecol. 2014; AUA 2012 metaanalysis and SUI Guidelines]. The most recent systematic review of long term studies by Tommaselli et al. 2015 shows that persistent or chronic pain -- defined as pain persisting beyond the perioperative period or reported at the last follow-up visit -- was 0.3% (13/3,974 Retropubic TVT patients) [Tommaselli GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015 Sep;26(9):1253-68]. These data are consistent with Nguyen et al's 2012 Kaiser Permanente database study: 0.02% (1/2,339 patients had an excision for pain); Unger et al's 2015 study: 0.2% (7/3,307 underwent sling revision due to vaginal pain/dyspareunia; Schimpf et al's 2014 SGS meta-analysis: 0%; Laurikainen et al's 2014 RCT of TVT versus TVT-O: no women required revision for dyspareunia; Svenningsen et al's 2013 10 year TVT prospective study: 0%; and Serati et al's 2012 10 year TVT prospective study: no women had de novo dyspareunia). Women presenting with dyspareunia or post-coital spotting following a mid-urethral sling should be evaluated for vaginal extrusion of the mesh sling.

XI. TVT in Unique Populations

TVT in women with mixed incontinence

Although TVT and TVT-O are not indicated for the treatment of urgency incontinence, studies have shown that TVT will relieve pre-existing urgency incontinence or urgency, many times in a majority of patients (>50%) [Nilsson et al. Int Urogynecol J. 2001]. For example, in the randomized controlled trial by Laurikanian et al, which compared

Ethicon's TVT and TVT-O devices, 84% of the women were cured of their preoperative urgency symptoms [Laurikainen E, Valpas A, Kivelä A, Kalliola T, Rinne K, Takala T, Nilsson CG. Retropubic compared with transobturator tape placement in treatment of urinary incontinence: a randomized controlled trial. Obstet Gynecol. 2007 Jan;109(1):4-11]. Similarly, in another study of TVT with 10 years follow up, it was noted that 63% of patients with mixed urinary incontinence before surgery indicated complete cure and were free of OAB symptoms at follow up [Aigmueller T, Trutnovsky G, Tamussino K, Kargl J, Wittmann A, Surtov M, Kern P, Frudinger A, Riss P, Bjelic-Radisic V. Ten-year follow-up after the tension-free vaginal tape procedure. Am J Obstet Gynecol. 2011 Nov;205(5):496.e1-5].

Women with mixed urinary incontinence often have relatively poorer neuromuscular function compared to those with pure stress incontinence. It is, therefore, not surprising that women with pure stress incontinence report greater improvement after mid-urethral sling surgery than those with mixed incontinence. However, both groups report substantial improvement in quality of life after mid-urethral sling placement [Balachandran A, Duckett J. Does the diagnosis of detrusor overactivity affect the long-term prognosis of patients treated with a retropubic midurethral sling? Int Urogynecol J. 2016 Dec;27(12):1913-1918]. De novo urgency and urgency incontinence are very rare following mid-urethral slings. The Urinary Incontinence Treatment Network's account of 2 year complications in the randomized trial of midurethral slings report no cases of de novo urgency incontinence in the retropubic group and 1 case (0.5%) in the transobturator group [Brubaker et al. AJOG 2011]. The prevalence of urgency incontinence in large epidemiologic studies, according to the ICS definition varies between 20% and 40%, and is known to increase with age. [Aigmueller T, Trutnovsky G, Tamussino K, Kargl J, Wittmann A, Surtov M, Kern P, Frudinger A, Riss P, Bjelic-Radisic V. Ten-year follow-up after the tension-free vaginal tape procedure. Am J Obstet Gynecol. 2011 Nov;205(5):496.e1-5] Longer term follow-up studies reporting de novo urgency incontinence following mid-urethral sling procedures must account for this

age-related onset of urgency incontinence symptoms.

TVT in the obese

Obesity is a known risk factor for urinary incontinence. Epidemiological studies demonstrate that there is a clear dose-response effect of weight on urinary incontinence, with each 5-unit increase in body mass index associated with a 20%-70% increase in risk of urinary incontinence [Whitcomb EL, Subak LL. Effect of weight loss on urinary incontinence in women. J Urol. 2011 Aug 1;3:123-32]. The odds of new onset urinary incontinence over 5-10 years increase by 30%-60% for each 5-unit increase in body mass index, with the association strongest for stress and mixed incontinence. These findings have several implications for the treatment of stress incontinence in the overweight or obese population. Given that obesity is a risk factor for stress incontinence and that sustained significant weight loss remains relatively rare, pelvic reconstructive surgeons have focused their attention on ascertaining whether stress incontinence surgery has similar outcomes in the obese population as the general population. As it is now considered gold standard surgical treatment of stress incontinence, the TVT device was utilized in many of these studies. In 2012, Killingsworth et al published a three-arm cohort of one year outcomes following TVT in normal weight, overweight, and obese women, reporting that stress incontinence symptoms were improved in all three BMI categories with no differences noted among groups [Killingsworth LB, Wheeler II TL, Burgio KL, Martirosian TE, Redden DT, Richter HE. One year outcomes of Tension-Free Vaginal Tape mid-urethral slings in overweight and obese women. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Sep; 20(9): 1103–1108]. Regardless of BMI category, patients had significant clinical improvement in stress and irritative symptoms, while reporting less bother and impact with urinary incontinence, with the majority being completely or somewhat satisfied (89-92%). Other studies that have examined the relationship between BMI and TVT sling outcome have found no association between BMI and sling failure [Raffi A, Darai E, Haab F, Samain E, Levardon M, Deval B. Body Mass Index and Outcome of Tension-Free Vaginal Tape.

European Journal Urology. 2003;43:288–292; Lovatsis D, Gupta C, Dean E, Lee F. Tension-free vaginal tape procedure is an ideal treatment for obese patients. Am J Obstet Gynecol. 003;189:1601–1605; Mukherjee K, Constantine G. Urinary stress incontinence in obese women: tension-free vaginal tape is the answer. BJU Int. 2001;88:881–883]. The effect of weight on stress incontinence raises the issue of longevity of the surgical results following TVT mid-urethral sling in obese patients and in patients whose BMI increases in the years following surgery. Few studies have addressed this question. In their 2007 retrospective questionnaire study, Hellberg et al did show that obesity may have an impact on effectiveness of TVT sling in the longer term [Hellberg D, Holmgren C, Lanner L, Nilsson S. The very obese woman and the very old woman: tension-free vaginal tape for the treatment of stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18:423–429]. They sent a questionnaire to 970 women who underwent a TVT sling between 1995 and 2001 and received a 78% response rate with an average follow up time of 5.7 years. They found a significant difference in failure rate between those subjects with a normal BMI (<25; 81.2% cure rate) and those with significant obesity (BMI>35; 52.1% cure rate). Results are limited by use of non-validated questionnaires, lack of assessment of the impact of incontinence on overall quality of life, and lack of reporting on any change in BMI between surgery and follow-up. Based on the evidence, the TVT mid-urethral sling is an effective surgical treatment for stress incontinence in the obese population, with symptom improvement and satisfaction with surgery rates similar to normal weight populations [Greer WJ, Richter HE, Bartolucci AA, Burgio KL. Obesity and pelvic floor disorders: a systematic review. Obstet Gynecol. 2008 Aug;112(2 Pt 1):341-9]. Longer term studies have shown that obese patients have good efficacy albeit slightly lower than non-obese patients, and pelvic reconstructive surgeons should counsel patients about the effect of weight on urinary incontinence symptoms [Aigmueller T, Trutnovsky G, Tamussino K, Kargl J, Wittmann A, Surtov M, Kern P, Frudinger A, Riss P, Bjelic-Radisic V. Ten-year follow-up after the tension-free vaginal tape procedure. Am J Obstet Gynecol. 2011 Nov;205(5):496.e1-5 (reporting 82% cure or improvement, 77% negative stress test, and 4.5% repeat anti-incontinence surgery at 10 years follow up)].

TVT in the elderly

Urinary incontinence is more common with advancing age and, especially in older women, has a multifactorial pathophysiology reflecting changes in the aging detrusor muscle, loss of muscle bulk and tone in the levator ani and urethral sphincter complex, impaired mobility, renal impairment and other comorbidities, side effects of medications, and progressive neurologic disease [DuBeau CE, Kuchel GA, Johnson T 2nd, Palmer MH, Wagg A. Incontinence in the frail elderly: report from the 4th International Consultation on Incontinence. Fourth International Consultation on Incontinence. Neurourol Urodyn. 2010; 29(1):165-78]. As the population ages, there has been more effort to characterize age-related outcomes for women undergoing mid-urethral sling procedures for stress urinary incontinence. In 2010, Stav et al. published the outcomes of a prospective comparative cohort study of 96 elderly women (≥ 80 years) compared with 1,016 patients younger than 80 and noted no difference in overall cure rate [Stav K, Dwyer PL, Rosamilia A, Schierlitz L, Lim YN, Lee J. Midurethral sling procedures for stress urinary incontinence in women over 80 years. Neurourol Urodyn. 2010 Sep; 29(7):1262-6]. Similar results were confirmed in 2011 by Groutz et al, who compared a cohort of 97 women 70 years of age or older to 256 younger women and found no difference in the rate of postoperative urodynamically confirmed stress incontinence, but a longer hospital stay and higher rate of postoperative urinary tract infections and overactive bladder symptoms in the older cohort [Groutz A, Cohen A, Gold R, Pauzner D, Lessing JB, Gordon D. The safety and efficacy of the "inside-out" trans-obturator TVT in elderly versus younger stress-incontinent women: a prospective study of 353 consecutive patients. Neurourol Urodyn. 2011 Mar;30(3):380-3].

Pelvic reconstructive surgeons should use careful clinical judgment in selecting appropriate elderly patients for anti-incontinence surgery. Large datasets from general, colorectal, vascular, and gynecology surgery demonstrate that age > 80 years is an independent predictor of adverse outcomes after surgery. [Toglia MR, Nolan TE.

Morbidity and mortality rates of elective gynecologic surgery in the elderly woman. Am J Obstet Gynecol. 2003 Dec;189(6):1584–7. discussion 1587-9]. Studies unique to pelvic floor disorders, such as Sung et al and Stepp et al reported on very small increases in the absolute risks of complications in older women after surgical treatment of pelvic floor disorders [Sung VW, Weitzen S, Sokol ER, Rardin CR, Myers DL. Effect of patient age on increasing morbidity and mortality following urogynecologic surgery. Am J Obstet Gynecol. 2006 May;194(5):1411–7; Stepp KJ, Barber MD, Yoo EH, Whiteside JL, Paraiso MF, Walters MD. Incidence of perioperative complications of urogynecologic surgery in elderly women. Am J Obstet Gynecol. 2005 May;192(5):1630–6]. This underscores the importance of careful patient selection and preoperative counseling in the elderly population prior to anti-incontinence surgery.

TVT and prior anti-incontinence surgery

The optimal management of recurrent or persistent stress urinary incontinence after an initial surgical failure is not known. Appropriate surgical treatment following a failed prior anti-incontinence surgery was identified as a leading question for investigation by the James Lind Alliance, a cohort of clinician and patient groups [Buckley BS, Grant AM, Tincello DG, Wagg AS, Firkins L (On behalf of the James Lind Alliance Priority Setting Partnership on Urinary Incontinence). Prioritizing research: patients, carers and clinicians working together to identify and prioritize important clinical uncertainties in urinary incontinence. Neurourology and Urodynamics 2010; Vol. 29, issue 5:708-14]. Palva and Nilsson published one of the first reports specific to repeat sling surgery in a group of 20 patients who had stress incontinence following a previous mid-urethral and reported cure or significant improvement rate of 75% [Palva K and Nilsson CG. Effectiveness of the TVT procedure as a repeat mid-urethra operation for treatment of stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Jul;20(7):769-74]. In a recently published retrospective multi-center chart review, Aberger et al reported on the outcomes of 224 consecutive patients undergoing placement of a retropubic mid-urethral sling or autologous rectus fascia pubovaginal sling after a prior failed mid-

urethral sling surgery [Aberger M, Gomelsky A, Padmanabhan P. Comparison of retropubic synthetic mid-urethral slings to fascia pubovaginal slings following failed sling surgery. Neurourol Urodyn. 2016 Sep;35(7):851-4]. Based on validated questionnaires, the subjective cure rate was 61.4%. A statistically significant improvement in pad use and in all validated questionnaire outcomes was observed for secondary repair with a retropubic midurethral sling and no significant differences in subjective cure rates or changes in postoperative questionnaire outcomes were noted between the midurethral sling and the fascial sling subgroups. These results are comparable to those published in 2013 by Verbrugge et al's review of a cohort of 80 women who underwent repeat midurethral sling surgery (33% transobturator, 31% retropubic, 20% minislings, 15% pelvicol biologic slings) with an overall 61% subjective cure rate and 74% subjective improvement [Verbrugghe A, De Ridder D, Van der Aa F. A repeat mid-urethral sling as valuable treatment for persistent or current stress urinary incontinence. Int Urogynecol J. 2013 Jun;24(6):999-1004]. When comparing different secondary sling types no difference was found in the overall continence rate, except for the pelvicol biological sling group, in which 7 out of 13 patients were not satisfied. In light of current evidence, pelvic reconstructive surgeons recognize that repeat surgery for stress incontinence is less likely to lead to a cure than primary surgery, that the specifics of each failure and the patient's clinical condition should be considered in choosing a subsequent procedure, and that patients should be carefully counseled about expected surgical outcomes. For many patients, the TVT procedure is a reasonable and effective secondary surgical option.

XII. Response to Claims by Plaintiff's Experts

Mechanical versus Laser cut mesh

The plaintiff's attorneys have claimed that mechanically cut mesh is inferior to laser cut mesh. Plaintiffs' experts claim that mechanical cutting, but not laser cutting, results in small residual particles that may induce an inflammatory cytotoxic host response. To my knowledge, there are no in-vivo studies to substantiate this claim. Laser cut mesh was

introduced in 2007 and there is no indication that the rate of mesh complications has dropped precipitously with its introduction. In fact, mesh complication rates, such as extrusion, are remarkably similar from early case series to later randomized surgical trials involving the TVT products. Following the introduction of laser cut mesh, Ethicon manufactures and sells both laser cut and mechanically cut TVT slings. There is no evidence to suggest that the edges of mechanically cut mesh cause complications. Moreover, as previously described in this report, the mesh sling is encased in a plastic covering which is removed after the sling is in position, minimizing the movement of mesh through the tissue.

I have also seen a company document suggesting that laser cut TVT mesh is 3 times stiffer than mechanically cut mesh when subjected to benchtop testing under strain. The suggestion is that stiffer mesh causes an increase in potential complications like mesh exposure and pain. Physical forces used in benchtop testing are not reflective of in vivo forces; however even if they were comparable, there is no evidence in the extensive clinical literature about the TVT devices to suggest that there is a difference in outcomes between mechanically cut and laser cut mesh. I do not rely on internal company emails to guide my evidence-based clinical decisions. Within the physiologic range, the meshes have no significant difference in strength or flexibility. Only when the mesh is stretched well beyond the forces experienced in vivo does the stiffness parameter change; however the TVT laser cut mesh is less stiff than mesh slings from other manufacturers [4.19.2006 Laser Cut Mesh for Gynecare TVT- CER Laser Cut Mesh ETH.MESH.00167104 - ETH.MESH.00167110; 12.14.2004 Memo regarding Company Test Stretching Laser Cut Mesh ETH.MESH. 01809080; 3.06.2006 Memo regarding Elongation Characteristics of Laser Cut Prolene Mesh for TVT ETH.MESH.01222075]. Moreover, photos of particles and stretching of the mesh after the needles and sheath are removed do not demonstrate in vivo application of the TVT and in any event the Prolene material has been demonstrated to be safe and effective (Prolene sutures and TVT Prolene mesh) in much larger volumes than particles shown

from this mechanical testing.

Plaintiffs' experts' opinions about a possible causal link between mesh that is mechanically cut or laser cut causing complications are an expression of their personal opinions that are not backed by scientific evidence. Detailed clinical data from implants using both the mechanically and laser cut meshes provide substantial opportunity to assess for any difference in outcomes. As previously stated, no such differences have been observed. Thus, any claim that such a warning is needed in the TVT IFU is without merit as this is not a risk.

Pore size and Mesh Weight

The plaintiffs' experts have claimed that a lighter weight, larger pore mesh would be better at reducing complications. The medical literature reviewed earlier in this report indicate that the TVT sling has a very low complication rate relative to other anti-incontinence procedures while providing excellent stress urinary incontinence symptom control and durability. In light of the available evidence, conscientious pelvic reconstructive surgeons who are driven by evidence-based medicine would require Level I evidence that a different mesh formulation than what is available in the TVT is substantially better prior to making a change from the current gold standard for clinical practice. To date, there is no evidence to suggest that lighter weight or larger pore mesh results in improved stress urinary incontinence symptom control or in a reduction in postoperative complications. The most widely accepted classification of mesh among the medical scientific community is the Amid classification system, which separates mesh into four categories based on the weave and porosity of the material [Amid, P.K. Hernia 1997]:

1. Type I mesh is monofilament macroporous. Macroporous is defined as pore size greater than 75 microns (μm). Based on current evidence, Type I mesh is considered to be the most suitable type for transvaginal placement. Pore size of 75 microns or

greater allows for optimal infiltration by macrophages, fibroblasts, neovascularization, and collagen deposition. The TVT Prolene mesh is a Type I mesh that has been shown in clinical trials and meta-analyses to have the highest biocompatibility with the lowest propensity toward infection or extrusion when compared with any other synthetic mesh material [Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;(7):CD006375].

2. Type II mesh consists of microporous mesh, defined as pore size less than 10μm. An example of this mesh type is Gore-Tex, which has been shown to have extrusion rates of 11%.

3. Type III mesh consists of a macroporous mesh with multifilaments or a microporous component, such as woven Dacron.

4. Type IV mesh is nanoporous, defined as pore size less than 1μm, and consists of submicronic and coated biomaterials, such as Silastic or dura mater substitute.

For the stress urinary incontinence application, the TVT Prolene mesh is a knitted, macroporous, monofilament light weight polypropylene and has been recognized by AUGS, SUFU, ACOG, SGS, and AAGL as a gold standard treatment for stress urinary incontinence due to its demonstrated long term durability, safety, and efficacy up to 17 years [2016 AUGS SUFU SGS AAGL ACOG Position Statement Mesh Midurethral Slings]. Mid-urethral slings are a 1 cm strip of mesh placed under the urethra; of these, the TVT Prolene mesh has the largest pore size. The pore size is approximately 1,300 microns, contrasted with > 75 microns to qualify as macroporous mesh, making it optimal for neovascularization and collagen deposition.

Multisite research studies that carried out comparisons of slings properties revealed that the Type I monofilament macroporous mesh that comprises the TVT has a unique tensile behavior of low stiffness and easy elongation, a combination which reduces

postoperative complications [Dietz HP, Vancaillie P, Svehla M, Walsh W, Steensma AB, Vancaillie TG. Mechanical properties of urogynecologic implant materials. Int Urogynecol J Pelvic Floor Dysfunct. 2003 Oct;14(4):239-43; Moalli PA, Papas N, Menefee S, Albo M, Meyn L, Abramowitch SD. Tensile properties of five commonly used mid-urethral slings relative to the TVT. Int Urogynecol J Pelvic Floor Dysfunct. 2008 May;19(5):655-63].

While plaintiffs' experts point to materials such as PVDF (Dynamesh), Ultrapro, Prolene Soft, or Vypro as safer alternatives to the TVT Prolene mesh, there is no data to support these claims. Whereas the TVT has been accepted as the gold standard treatment only after decades of large case series, randomized surgical trials comparing it to native tissue operations and other synthetic slings, and meta-analyses supporting its efficacy and safety, there is minimal data on the application of the meshes advocated for by plaintiffs' experts to the treatment of stress urinary incontinence. For example, Dr. Rosenzweig points to a study by Okulu et al and hypothesizes that Ultrapro is a better sling material [Okulu E, Kayigil O, Aldemir M, Onen E. Use of three types of synthetic mesh material in sling surgery: a prospective randomized clinical trial evaluating effectiveness and complications. Scand J Urol. 2013 Jun;47(3):217-24]. However, the materials in this small study (group I (n = 48), Vypro mesh; group II (n = 48), Ultrapro mesh; and group III (n = 48), Prolene light mesh) were not evaluated against the TVT and the surgical technique and mesh implantation used in the Okulu study is very different from the TVT:

"An incision with an inverted "A" shape was made on the anterior wall of the vagina. The upper part of the A-shaped incision was formed into an island belonging to the vaginal wall. This patch was 3 x 4 cm in most of the patients. The proximal anterior vaginal wall (the lower part of the "A") was dissected as a flap (Figure 2a)". By comparison, the TVT is implanted through a single small 1-1.5 centimeter incision under the midurethra and does not require an A incision, making a large vaginal wall island, or the creation of

vaginal flaps. The procedure is further described as:

"The size of the mesh was individualized during the procedure". By comparison, the TVT sling is a standardized mesh strip 1.1 centimeters in width, placed under the midurethra. Furthermore, the mesh placement technique described by Okulu et al is a tensioned technique that relies on prolene suture to attach the mesh strip to the rectus fascia. Most importantly, the Okulu procedure required a two day hospitalization with an indwelling foley catheter that was not removed until the second postoperative day. Relative to the TVT, which is a 30 minute outpatient procedure that rarely requires prolonged catheterization, this technique is a step backwards in the treatment of stress urinary incontinence in women. Even in this very small study with short-term (48 months) follow-up, the authors report mesh exposure rates of 4.3% with Vypro, the lightest weight and largest pore mesh included in the study, 2.1% with Ultrapro mesh, and 4.3% with Prolene Soft mesh. By comparison, based on numerous randomized trials and metaanalyses of the TVT sling, the rates of exposure are most reliably in the 1-2% range, despite significantly longer follow up than the 48 months described by Okulu et al. Due to the small numbers and limited follow-up, this study does not constitute data to establish that these meshes are effective, safe, or have reproducible results and certainly cannot be interpreted to mean that they are equally effective substitutes for TVT.

PVDF and Dynamesh are not used in the United States to treat stress urinary incontinence and these materials have not been demonstrated by reliable clinical data to be safer or more effective than TVT.

I have also reviewed documents that show that when a lighter weight partially absorbable mesh was being researched by Ethicon for the sling application, the majority (two thirds) of surgeons declined to use this mesh, while the remaining one-third were cautious optimists who could speculate about potential benefits, but wanted to see at

least two years of clinical data before considering use [ETH.MESH.02219584 - Scion PA-SUI Treatment Unmet Needs Exploratory Research January 22, 2010]. It was noted that physicians were very confident and comfortable in their use of the TVT midurethral sling and they were very concerned that using less material (lighter weight, larger pore size, partially absorbable mesh) would ultimately lead to more failures (recurrent stress urinary incontinence) over longer term follow up.

As outlined in this report, the TVT procedure has the largest amount of medical evidence of any anti-incontinence procedure supporting its short- and long-term efficacy, safety, and durability. There are no large or rigorously designed multi-center randomized surgical trials showing either short- or long-term outcomes or superiority of lighter weight or larger pore mesh for treatment of stress urinary incontinence and TVT remains the gold standard in treatment.

Cytotoxicity

Plaintiffs' experts have made claims that the TVT mesh results in an untoward foreign body response, and that the mesh is cytotoxic. However, the reliable data cited in my report dispels these claims. There are numerous level 1 systematic reviews and metaanalyses that demonstrate the TVT sling is the most biocompatible mesh material for the surgical treatment of stress urinary incontinence and has a predictable foreign body response with a low complication rate [Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;(7):CD006375; Schimpf MO, Rahn DD, Wheeler TL, Patel M, White AB, Orejuela FJ, El-Nashar SA, Margulies RU, Gleason JL, Aschkenazi SO, Mamik MM, Ward RM, Balk EM, Sung VW; Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014 Jul;211(1):71.e1-71.e27; Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling

operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006375; Dmochowski RR, Blaivas JM, Gormley EA, Juma S, Karram MM, Lightner DJ, Luber KM, Rovner ES, Staskin DR, Winters JC, Appell RA; Female Stress Urinary Incontinence Update Panel of the American Urological Association Education and Research, Inc., Whetter LE. Update of AUA guideline on the surgical management of female stress urinary incontinence. J Urol. 2010 May;183(5):1906-14].

Any surgical incision and dissection constitutes a controlled wound that leads to the expected physiologic response to injury: hemostasis, inflammation, proliferation and neovascularization, and scar remodeling, leading to the generation and reorganization of scar tissue. A foreign body host response is expected with the introduction of any foreign body, whether it is suture or mesh. The data discussed in this report have shown that the use of a Type 1 macroporous monofilament mesh leads to the most optimal wound healing, collagen deposition, and minimization of infection. The ingrowth of host tissue through the thin strip of TVT mesh at the midurethra leads to its long term efficacy and durability in treating stress incontinence.

In the development and optimization of the TVT's design, Ulmsten and Petros carried out numerous animal and human studies to evaluate a variety of materials including Gore-Tex, Mersilene, and Dacron. Their results led to the use of the permanent Prolene polypropylene mesh placed at the midurethra as the superior and optimal material [Petros PE, Ulmsten UI. An integral theory of female urinary incontinence. Experimental and clinical considerations. Acta Obstet Gynecol Scand Suppl. 1990;153:7-31; Petros PE, Ulmsten UI. An integral theory and its method for the diagnosis and management of female urinary incontinence. Scand J Urol Nephrol Suppl. 1993;153:1-93; Ogah J, Cody DJ, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. Neurourol Urodyn. 2011 Mar;30(3):284-91; Petros P. Creating a gold standard surgical device: scientific discoveries leading to TVT and beyond: Ulf Ulmsten

Memorial Lecture 2014. Int Urogynecol J. 2015 Apr;26(4):471-6].

When compared to other materials, the TVT has been shown to be very well tolerated in studies that analyzed the tissue of stress incontinent women after implantation of mesh materials [Falconer C, Söderberg M, Blomgren B, Ulmsten U. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12 Suppl 2:S19-23]. There was practically no inflammatory tissue reaction seen 2 years after TVT placement when Prolene mesh was used. No change in collagen extractability (a by-proxy measure of tissue friability or fragility) was found in the Prolene group. Moreover, there was no histological difference between paraurethral connective tissue in biopsies from patients operated on with Prolene tape and in controls 2 years after surgery.

These translational research outcomes correlate with the robust long-term clinical outcomes following TVT placement in various cohorts of patients with primary SUI, recurrent SUI, ISD, and mixed incontinence [Falconer C, Söderberg M, Blomgren B, Ulmsten U. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12 Suppl 2:S19-23; Nilsson CG, Kuuva N. The tension-free vaginal tape procedure is successful in the majority of women with indications for surgical treatment of urinary stress incontinence. BJOG. 2001 Apr;108(4):414-9; Rezapour M, Ulmsten U. Tension-Free vaginal tape (TVT) in women with recurrent stress urinary incontinence--a long-term follow up. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12 Suppl 2:S9-11; Cox A, Herschorn S, Lee L. Surgical management of female SUI: is there a gold standard? Nat Rev Urol. 2013 Feb;10(2):78-89; Nilsson CG, Palva K, Aarnio R, Morcos E, Falconer C. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265-9; Nilsson CG. Creating a gold standard surgical procedure: the development and implementation of TVT : Ulf Ulmsten Memorial Lecture 2014. Int Urogynecol J. 2015 Jun;26(6):787-9; Tommaselli

GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015 Sep;26(9):1253-68].

The claim that the TVT Prolene mesh is cytotoxic is based on discrepant cell line testing that was submitted with the TVT 510k. However, it was noted that the clinical data in humans show that this is an aberration, later determined to be due to an increased surfactant (PROCOL LA 10) concentration during autoclaving to which the closed system of the in vitro assay test was susceptible, and the mesh is not cytotoxic in patients [1997 Cytotoxicity risk assessment for the TVT (Ulmsten device) ETH.MESH.00349228; Follow up testing on mechanisms of cytotoxicity ETH.MESH.02134271].

This discrepant aberration specific to the closed in vitro cell line in the ISO elution testing is refuted by the extensive clinical data specific to the TVT device, which shows that the TVT mesh is not cytotoxic in patients. If the mesh were indeed cytotoxic there would not be evidence of tissue incorporation, but rather of tissue necrosis upon exposure to a cytotoxic material. Instead, the clinical data shows excellent tissue incorporation and long term biocompatibility and durability. Dr. Rosenzweig postulates that cytotoxicity causes mesh exposure, but the clinical data do not support this speculative conclusion. Moreover, as shown in this report, the high level short, medium and long term data show that the TVT has the lowest exposure rate (1-2%), even with long term follow-up [Kuuva N, Nilsson CG. A nationwide analysis of complications associated with the tension-free vaginal tape (TVT) procedure. Acta Obstet Gynecol Scand. 2002 Jan;81(1):72-7; Ogah J, Cody DJ, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. Neurourol Urodyn. 2011 Mar;30(3):284-91; Svenningsen R, Staff AC, Schiøtz HA, Western K, Kulseng-Hanssen S. Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J. 2013 Aug;24(8):1271-

8; Schimpf MO, Rahn DD, Wheeler TL, Patel M, White AB, Orejuela FJ, El-Nashar SA, Margulies RU, Gleason JL, Aschkenazi SO, Mamik MM, Ward RM, Balk EM, Sung VW; Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014 Jul;211(1):71.e1-71.e27; Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;(7):CD006375; Tommaselli GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015 Sep;26(9):1253-68].

Mesh Degradation

SEM analyses of explanted slings have noted superficial cracking of some samples of polypropylene [Clavé A, Yahi H, Hammou JC, Montanari S, Gounon P, Clavé H. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J. 2010 Mar;21(3):261-70]. This finding has raised claims of mesh degradation; however, it has been shown that this surface cracking is most likely biologic in origin and does not represent cracking of the polypropylene [Thames SF, White JB, Ong KL. The myth: in vivo degradation of polypropylene-based meshes. Int Urogynecol J. 2016 Sep 6. [Epub ahead of print] PubMed PMID: 27600700]. Findings on SEM pictures must be correlated clinically in order to avoid arriving at erroneous conclusions [Sibai BM, Spinnato JA. Hydatoxi Lualba: artifact produced by sulfation. Am J Obstet Gynecol. 1983 Dec 1;147(7):854].

While Plaintiffs' experts have hypothesized that these surface changes may lead to complications or adverse outcomes, these hypotheses are not supported by clinical outcomes published in the extensive peer-reviewed literature related to TVT cited in my report. Numerous prospective studies have followed patients for 5 to 17 years following

TVT placement and show excellent durability, utility and safety of the TVT device [2013 AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of SUI; 2014 AUGS SUFU FAQs for Providers; Nilsson CG, Palva K, Aarnio R, Morcos E, Falconer C. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265-9; Tan PF, Yang LL, Ou RB, Tang P, Yang WJ, Huang JB, Wei W, Wei XH, Wang B, Xie KJ. Effectiveness and complication rates of tension-free vaginal tape, transobturator tape, and tension-free vaginal tape-obturator in the treatment of female stress urinary incontinence in a medium- to long-term follow up. Meta-analysis of randomized controlled trials. Saudi Med J. 2014 Jan;35(1):20-32; Tommaselli GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015 Sep;26(9):1253-68; 2016 AUGS SUFU SGS AAGL ACOG Position Statement Mesh Midurethral Slings].

Claims Regarding Carcinogenicity and Sarcoma Formation

Claims that polypropylene midurethral slings and TVT in particular may be carcinogenic have been made by Plaintiffs' experts. However, these claims are based on speculative, unreliable and improperly extrapolated rodent data, while the reliable human data refutes and is inconsistent with this claim. Plaintiffs' experts point to polypropylene MSDS (Material Data Safety Sheet) and the statement "COMPONENT TOXICITY: Polypropylene has been tested in laboratory rats by subcutaneous implantation of discs or powder. Local sarcomas were induced at the site of implantation" [Sunoco MSDS]. However, MSDS are pertinent to the manufacturing of raw unprocessed and unsterilized polypropylene for the protection of workers as required by OSHA and are not relevant to the finished medical device and not intended for general consumer use or as a product design document [Moalli P, Brown B, Reitman MT, Nager CW. Polypropylene mesh: evidence for lack of carcinogenicity. Int Urogynecol J. 2014 May;25(5):573-6].

Plaintiffs' experts point to studies in the rodent where smooth samples of polypropylene (discs and sheets) led to sarcoma formation. However, Prolene polypropylene mesh is not provided in sheet or disc form. Prolene polypropylene and TVT mesh is a processed, finished, and sterilized device. TVT Prolene polypropylene mesh is comprised of a macroporous, knitted Type 1 mesh [2014 AUGS SUFU Provider FAQs by Providers MUS for SUI]. Prolene polypropylene was tested in the animal model [Two year tissue reaction studies in the rat and dog. NDA 16-37; Vol. 1.1, Report date 10/14/1965] and found to be non-carcinogenic in connection with its NDA that was approved by the FDA after it found that the finished product was safe and effective [ETH.MESH.00349236-37]. Additionally, more recent animal studies have evaluated monofilament and multifilament polypropylene mesh implantation in the subcutaneous tissues of mice and did not show any sarcoma formation during 2 years of follow-up [Witherspoon P, Bryson G, Wright DM, Reid R, O'Dwyer PJ. Carcinogenic potential of commonly used hernia repair prostheses in an experimental model. Br J Surg. 2004 Mar;91(3):368-72]. The phenomenon of sarcoma formation in some rodents in response to implantation of smooth and nonporous materials but not in response to knitted porous polypropylene mesh can be explained by the "Oppenheimer effect". Oppenheimer showed that while inert materials (glass and inert metals) implanted as discs and sheets might induce sarcomas, the porous forms of these materials would not induce sarcoma in the same species. Plaintiffs' experts' speculative presumption that discrepant rodent data using an unfinished and different form of polypropylene is transferrable to humans and the finished product is an unscientific leap.

In their claims that polypropylene mesh is carcinogenic, the plaintiffs' experts cite individual case reports. Isolated case reports are not evidence of an association or causation. The potential risk of carcinogenicity of polypropylene midurethral slings has been examined in humans in large epidemiologic studies involving cohorts of over 2,200 patients and the results do not show a carcinogenic effect. Linder et al evaluated a

cohort of 2,474 women who had undergone MUS at the Mayo Clinic and found 51 patients with cancer diagnoses, of which 49 were pre-existing conditions (Background rate 1.98%, 49 out of 2,474) [Linder BJ, Trabuco EC, Carranza DA, Gebhart JB, Klingele CJ, Occhino JA. Evaluation of the local carcinogenic potential of mesh used in the treatment of female stress urinary incontinence. Int Urogynecol J. 2016 Sep;27(9):1333-6]. There were only two cases of neoplasia occurring after MUS placement (0.08 %, 2 out of 2,474) at a median follow up of 60 months. With regard to these two cases, the authors concluded that "it is unlikely that the subsequent development of a vaginal melanoma or ovarian tumor is due to the synthetic sling, given the sling position and pathological condition identified". Importantly, there were no sarcomas, squamous cell carcinomas, bladder, or urethral cancers detected following synthetic MUS procedures. The authors also found that in this 2,474 cohort "64 patients (2.6 %) underwent repeat surgery for vaginal mesh exposure; however, the 2 patients with confirmed malignancies did not have vaginal mesh exposures. Additionally, no local cancers were detected among the 302 patients (12% of cohort) with more than 10 years' follow-up."

Similar results were seen by King et al who evaluated 2,361 patients who had undergone polypropylene MUS placement at the Cleveland Clinic for an average follow-up of 42 months, and some patients as long as 122 months [King AB, Zampini A, Vasavada S, Moore C, Rackley RR, Goldman HB. Is there an association between polypropylene midurethral slings and malignancy? Urology. 2014 Oct;84(4):789-92]. They found that of the 2,361 women (0.08%) one had developed bladder cancer and one developed a vaginal cancer; neither were determined to be related to the sling in light of the location and cell type. No sarcomas were found. The authors concluded that their series does not support any association between polypropylene mesh used for midurethral slings and the development of malignancy in humans.

Both Linder and King et al report that the rate of tumor detection in their cohorts is

consistent with the expected rate of neoplasia development in the general population. As noted by Linder et al "given the rarity of local cancer diagnoses following sling placement, in both our series and previous studies, we would agree with a recent commentary stating that if there is concern about the association between polypropylene midurethral sling placement and cancer formation, it must be demonstrated by more than case reports. As there are a large number (i.e., millions) of women who have undergone midurethral sling placement, it is not surprising that some patients experience new cancer diagnoses, as these may occur in any cohort followed over time." King et al. note that "Midurethral slings have been well studied, with follow up of 17 years. The literature suggests that these procedures are not only successful but also safe." Robust clinical studies refute the claims of carcinogenicity of the TVT sling; it is not carcinogenic. Overall, as noted above I do not find there to be reliable evidence establishing the above claims and as noted later, it is my opinion that there would not be a need to warn of these claimed risks.

Biologic Materials - Cadaveric and Xenograft

Some of plaintiffs' experts have claimed that using a biologic graft made of cadaveric or xenograft (animal) material would be safer and more effective but this has not been demonstrated. As discussed below, biologic grafts were evaluated in the 1990s to the early 2000 time period by various physicians and due to high adverse event rates, questionable integration, bacterial and virus transmission (hepatitis, HIV, etc.) low efficacy and durability, and issues with costs and supply they were not adopted by many surgeons or patients.

The first use of a cadaveric suburethral sling (allogenic fascia lata) to treat stress urinary incontinence was reported in 1996 by Handa in a cohort of 16 women with follow up ranging from 6 months to 1 year [Handa VL, Jensen JK, Germain MM, Ostergard DR. Banked human fascia lata for the suburethral sling procedure: a preliminary report.

Obstet Gynecol. 1996 Dec;88(6):1045-9]. Handa noted that autologous slings must be prepared during the operative procedure, which can increase operative time and requires a substantially larger incision (or a second incision), resulting increased morbidity (including postoperative pain") and may decrease the cosmetic acceptability of the procedure. Gore-tex slings had been reported to have higher rates of sinus tract formation and erosion. And, as a result, beginning in 1994, the authors offered patients three options for suburethral slings: autologous fascia, Gore-tex synthetic slings and the cadaveric fascia. Notably, as discussed earlier in my report, autologous and Gore-tex synthetic suburethral slings are much more invasive, have more wound complications, more voiding dysfunction, and, as first line surgical treatment for stress incontinence, are inferior to the TVT which would come a few years later.

Per Handa, the cadaveric slings were fashioned in a strip that was 2.5 cm wide and placed at the proximal urethra (unlike the midurethral placement of a narrow 1cm wide TVT). Notably, there were wound complications in three of the 16 (18.75%) patients with two patients (12.5%) having abdominal wound infections that required treatment and drainage, and one additional patient (6.25%) who had an asymptomatic cadaveric sling exposure at 6 weeks follow up that resolved. There was significant voiding difficulty, with postoperative bladder drainage required for a mean of 29 days (range 4-187) and 50% of women did not experience a return of adequate voiding function within two weeks. One patient continued to experience incomplete voiding at 187 days, requiring intermittent self-catheterization. Detrusor instability resolved in one of four cases and arose de novo in 36% of cases. The objective cure rate was 79% and the subjective cure rate was 86%, reported to be satisfactory by Handa when one considers the performance of this small cohort of cadaveric slings against the invasiveness and morbidity of autologous and Gore-tex slings. However, as can be seen above, the use of cadaveric material led to higher wound complications, more voiding dysfunction and more de novo detrusor instability than the high level, reliable data shows with TVT, while objective cure in the short follow up is inferior to TVT. These data on cadaveric

slings do not demonstrate that it is a feasible, safer or more effective alternative to the TVT.

Following Handa's publication, other surgeons investigated the use of cadaveric slings and supporting her report of decreased efficacy, inferior material performance, lack of durability and safety concerns. Fitzgerald reported on a cohort of 32 patients who underwent suburethral sling placement with fascia allograft and found only a 69% cure rate at 3 months [Fitzgerald MP, Mollenhauer J, Brubaker L. Failure of allograft suburethral slings. BJU Int. 1999 Nov;84(7):785-8]. Moreover, 8 patients (25%) with persistent or recurrent stress incontinence requested revision of their allograft slings. The allograft was present but grossly degenerated in two (6%) patients and completely absent in five additional (14%) patients, leading the authors to strongly caution against the use of cadaveric fascia lata in slings. Unlike TVT, which was studied in animal models and then in clinical studies before it release to the market, the authors noted that the "use of allograft in gynecological surgery has not been preceded by any published animal models and the fate of implanted donor fascia in this setting is currently unknown."

Ultimately cadaveric slings would be assessed in animal models and the results were not positive. Dora evaluated 15 rabbits randomized into three survival groups (2, 6 and 12 weeks) and each rabbit had human cadaveric fascia, porcine dermis, porcine small intestine submucosa, polypropylene mesh, and autologous fascia implanted on the anterior rectus fascia [Dora CD, Dimarco DS, Zobitz ME, Elliott DS. Time dependent variations in biomechanical properties of cadaveric fascia, porcine dermis, porcine small intestine submucosa, polypropylene mesh and autologous fascia in the rabbit model: implications for sling surgery. J Urol. 2004 May;171(5):1970-3]. At harvest, tensiometry and image analysis were performed on each sling. All of the materials except polypropylene mesh and autologous fascia had a time dependent significant decrease in tensile strength with human cadaveric fascia and porcine allografts having a marked

decrease (60% to 89%) in tensile strength and the force necessary to elongate the sling. The autologous sling had the greatest reduction of surface area at 50% followed by SIS porcine, cadaveric fascia, porcine dermis, and polypropylene mesh had the least. The authors noted that the "biomechanical results of the current study support the use of polypropylene mesh for sling surgery relative to other nonautologous materials."

Krambeck followed up with a study of 10 rabbits each having human cadaveric fascia, porcine dermis, porcine small intestine submucosa, polypropylene mesh and autologous fascia implanted on the anterior rectus fascia to assess inflammation and scar formation [Krambeck AE, Dora CD, Sebo TJ, Rohlinger AL, DiMarco DS, Elliott DS. Time-dependent variations in inflammation and scar formation of six different pubovaginal sling materials in the rabbit model. Urology. 2006 May;67(5):1105-10]. The study showed a high degree of fibrosis and low inflammation with the polypropylene mesh which was similar to autologous fascia, while a low to moderate degree of fibrosis and high inflammation was seen with both xenograft materials, and a degree of high fibrosis and inflammation was seen with both human cadaveric fascias.

Woodruff later published a study comparing graft materials from 24 women undergoing sling revision (polypropylene mesh (PPM) in 10, autologous fascia in 5, porcine dermis in 4, cadaveric dermis in 3, and cadaveric fascia in 2) [Woodruff AJ, Cole EE, Dmochowski RR, Scarpero HM, Beckman EN, Winters JC. Histologic comparison of pubovaginal sling graft materials: a comparative study. Urology. 2008 Jul;72(1):85-9]. The study found no graft degradation had occurred in the polypropylene mesh, while autologous and cadaveric fascia had the most demonstrable graft degradation. Additionally, the cadaveric fascia displayed progressive degradation over time. There was no encapsulation with autologous fascia or polypropylene mesh, while the porcine dermis was the most encapsulated, and the cadaveric grafts had mild to moderate encapsulation. Additionally, no host infiltration had occurred with the encapsulated

porcine grafts and only peripheral infiltration of fibroblasts had occurred in the cadaveric grafts and no neovascularization. The polypropylene grafts had the greatest number of fibroblasts throughout the entire graft and best neovascularity. The mesh graft was noted to be infiltrated with host tissue. A foreign body reaction was visible microscopically with the polypropylene, but there was no gross evidence of graft disruption or adverse effects on the host because of this foreign body reaction. Additionally, no infection was seen.

Fitzgerald et al followed their cadaveric sling cohort mentioned earlier beyond the 3 month visit (n=27) and found that 14 (52%) sling procedures were failures, with recurrent SUI symptoms experienced between 2 weeks and 24 months after the procedure [FitzGerald MP, Edwards SR, Fenner D. Medium-term follow-up on use of freeze-dried, irradiated donor fascia for sacrocolpopexy and sling procedures. Int Urogynecol J Pelvic Floor Dysfunct. 2004 Jul-Aug;15(4):238-42]. By one year post op, 41% of the slings were known to be failures. Of the 14 failures, 10 patients (37%) elected to undergo repeat incontinence surgery. The authors also reported on the use of the cadaveric material in a sacral colpopexy cohort (n=53) and found 83% of patients experienced failure at a median of 12 months after surgery and 40% opted for reoperation.

The authors note that the “unacceptably high failure rates for sacral colpopexy and pubovaginal sling reported in this series indicate failure of the graft material and are well below the usual 5%–15% failure rates reported by this group and many others when using synthetic or autograft material for the same surgical procedures. Further, the inability to find any remaining graft material at the time of reoperation in the majority of patients confirms degradation and resorption of the fascial graft.” Additional concerns were noted, such as variation in results due to donor location, differing procurement and processing of the cadaveric material, and other issues such as the fact that a surgeon cannot assume that they are using the same tissue that another surgeon used or that

results reported at 1 year will hold over time.

The authors also noted that their results were similar to Soergel et al, who used freeze-dried, irradiated cadaveric fascia lata and reported only a 33.3% success rate at a mean follow up of 12.2 weeks, with the sling material strongly associated with surgical outcome after controlling for all confounding variables ($p < 0.00005$) [Soergel TM, Shott S, Heit M. Poor surgical outcomes after fascia lata allograft slings. Int Urogynecol J Pelvic Floor Dysfunct. 2001; 12(4):247-53]. Like Fitzgerald et al, Soergel et al also concluded that fascia lata allografts are a poor choice for pubovaginal slings. Fitzgerald et al further cautioned that although some other case series using tissue that is freeze dried but not irradiated may lead to better results in shorter term follow up, more surgical failures are being seen with longer and more careful follow-up [O'Reilly K, Govier FE. Intermediate term failure of pubovaginal slings using cadaveric fascia lata: A case series. J Urol 2002; 167:1356–58].

Like Fitzgerald et al, Kammerer-Doak reported on a cohort of patients treated with cadaveric material for slings (n=22) and sacralcolpopexy (n=11) [Kammerer-Doak DN, Rogers RG, Bellar B. Vaginal erosion of cadaveric fascia lata following abdominal sacrocolpopexy and suburethral sling urethropexy. Int Urogynecol J Pelvic Floor Dysfunct. 2002;13(2):106-9]. For the sling procedure, a 2x22 cm graft was brought through the retropubic space with the ends overlapped above the fascia. The authors found vaginal erosion of cadaveric fascia lata graft in 5 (23%) following the sling procedure and 3 (27%) following sacrocolpopexy, which was diagnosed at a mean of 36.8 days after surgery. Four of the 8 (50%) underwent excision of the exposed graft and an additional patient requiring trimming of the exposed cadaveric graft in the office. Postoperative febrile morbidity was significantly associated with cadaveric graft erosion (Table 2, $p=0.04$).

Meanwhile, in 2001 Carbone reported on a cohort of 154 consecutive patients who underwent a bone anchored, cadaveric fascia pubovaginal sling procedure by a single surgeon from July 1998 to June 1999 and found that 40% had recurrent stress urinary incontinence with the vast majority graded as moderate or severe [Carbone JM, Kavaler E, Hu JC, Raz S. Pubovaginal sling using cadaveric fascia and bone anchors: disappointing early results. J Urol. 2001 May;165(5):1605-11]. Of these, 26 patients had a second anti-incontinence procedure, for a reoperation rate of 16.9% and the average time to reoperation was 9 months (range 3 to 15). Additionally, intraoperative findings at reoperation in these 26 patients showed that uniformly all of the allogeneic cadaveric fascia used for sling material appeared to be fragmented, attenuated or simply absent at reoperation. The results showing a breakdown of the cadaveric material led to the abandonment of the use of cadaveric fascia allografts in all pubovaginal slings at their institution.

The authors noted the great uncertainty and conflicting data with cadaveric slings including Secrest and White who reported an 86% positive outcome rate with the use of autologous fascial slings as compared to only 65% with allograft fascial materials [Secrest CL. White, PC. Comparison of autologous and allograft fascia in pubovaginal sling for stress urinary incontinence. J Urol 2000; Suppl.163:165, abstract 732]. As further concern, they observed:

“Consideration must be given to the source of the cadaveric fascia. While all tissue banks followed FDA guidelines for harvesting and preparation of the fascia, no control was set on the quality of fascia obtained. No consideration was given to the sex of the donor, age of the fascia or thickness of graft. Despite folding of the sling to double the thickness, clear variations in the quality of the cadaveric tissue were evident at reconstitution. Although it was our impression that we were using material that we thought was strong enough to support the urethra and bladder neck, it is unclear if any of these variations in the quality of the grafts were related to or could predict the

ultimate failure of the material."

Huang reported on a cohort of 18 women who underwent cadaveric sling placement for stress urinary incontinence and found that five patients (28%) had significant failure with full recurrence of incontinence within 3 to 6 months [Huang YH, Lin AT, Chen KK, Pan CC, Chang LS. High failure rate using allograft fascia lata in pubovaginal sling surgery for female stress urinary incontinence. Urology. 2001 Dec;58(6):943-6]. Like other surgeons, because of the unacceptably high failure rate in such a short period, Huang et al stopped using allograft as a sling material.

All of this leads to the uncertainty and concern by many surgeons who elect to not use cadaveric and xenograft materials and is additional evidence of why these materials are not a feasible, safer or more effective alternative than TVT. Additionally as testing became more sophisticated, there arose a risk of prion and DNA transmission with cadaveric materials (such as dermis and fascia) which made these materials undesirable in the field [Hathaway JK, Choe JM. Intact genetic material is present in commercially processed cadaver allografts used for pubovaginal slings. J Urol. 2002 Sep;168(3):1040-3; Choe JM, Bell T. Genetic material is present in cadaveric dermis and cadaveric fascia lata. J Urol. 2001 Jul;166(1):122-4].

Moreover, among the various materials for implantation as a sling, TVT has shown the best efficacy and safety balance and like autologous material, cadaveric and xenograft slings have not been shown to be superior per the Cochrane Reviews [Rehman H, Bezerra CC, Bruschini H, Cody JD. Traditional suburethral sling operations for urinary incontinence in women. Cochrane Database Syst Rev. 2011 Jan 19;(1):CD001754; Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006375; Dmochowski RR, Blaivas JM, Gormley EA, Juma S, Karram MM,

Lightner DJ, Luber KM, Rovner ES, Staskin DR, Winters JC, Appell RA; Female Stress Urinary Incontinence Update Panel of the American Urological Association Education and Research, Inc., Whetter LE. Update of AUA guideline on the surgical management of female stress urinary incontinence. J Urol. 2010 May;183(5):1906-14; Revised 2012 downloaded at https://www.auanet.org/common/pdf/education/clinical-guidance/Incontinence.pdf].

In summary, cadaveric and xenograft materials have not been shown to be a feasible replacement for TVT due to their low efficacy rate, short-lived durability, and high complication rates. The evidence does not show that they are safer or more effective than TVT. Trends in the use of the midurethral sling show that it is the preferred method to treat stress urinary incontinence by over 95% of pelvic surgeons while less than 5% use biologic slings as their primary repair method, which is consistent with the high level of data supporting TVT as opposed to the very limited, discrepant and disconcerting data regarding biologic slings [Clemons JL, Weinstein M, Guess MK, Alperin M, Moalli P, Gregory WT, Lukacz ES, Sung VW, Chen BH, Bradley CS; AUGS Research Committee. Impact of the 2011 FDA transvaginal mesh safety update on AUGS members' use of synthetic mesh and biologic grafts in pelvic reconstructive surgery. Female Pelvic Med Reconstr Surg. 2013 Jul-Aug;19(4):191-8; Chughtai BI, Elterman DS, Vertosick E, Maschino A, Eastham JA, Sandhu JS. Midurethral sling is the dominant procedure for female stress urinary incontinence: analysis of case logs from certifying American Urologists. Urology. 2013 Dec;82(6):1267-71].

TVT Instructions for Use

I have reviewed the claims by Plaintiffs' experts suggesting that the TVT IFU fails to warn surgeons of certain risks. However, it is my opinion that the risks supposedly not mentioned explicitly in the IFU are not true risks as earlier noted, they are risks that are common to stress urinary incontinence and vaginal surgery and are basic risks that are

fundamental knowledge in the field, or they were warned of given the language of the IFU by the intended reader, the pelvic surgeon.

Importantly, the TVT IFU states that it is not a comprehensive reference to surgical technique for correcting Stress Urinary Incontinence. The device should be used only by physicians trained in the surgical treatment of Stress Urinary Incontinence and specifically in implanting the TVT device. These instructions are recommended for general use of the device. Variations in use may occur in specific procedures due to individual technique and patient anatomy." Additionally, Professional Education material and risk information supplements the IFU which further states, "WARNINGS AND PRECAUTIONS: Users should be familiar with surgical technique for bladder neck suspensions and should be adequately trained in implanting the GYNECARE TVT system before employing the GYNECARE TVT device. It is important to recognize that GYNECARE TVT is different from a traditional sling procedure in that the tape should be located without tension under midurethra."

Pelvic surgeons knowledgeable of bladder neck suspension incontinence surgery would be educated and trained on the potential risks with the surgeries. These risks include the elemental risks of bleeding events (such as hemorrhage, hematoma and the need for transfusion), injury to organs (such as the bladder and lower urinary tract, nerves and vessels), voiding dysfunction (frequency, interrupted voiding, urinary hesitancy), retention, detrusor instability (urgency, urge incontinence, frequency), infection, wound complications such as poor tissue healing, seroma, abdominal incision hernia, suture and graft exposure and erosion, secondary site harvest complications and morbidity, vaginal and pelvic pain and dyspareunia, inflammation, fistula, anesthesia risks, cardio and pulmonary risk (DVT and PE, as well as death), scarring, failure, the need for surgical treatment and reoperation, and that symptoms and complications can fall within a spectrum of asymptomatic to mild, moderate and severe and can be acute or chronic. Mesh exposure and erosion are the only unique risks with the use of TVT compared to

other stress urinary incontinence surgeries and as shown earlier, there are other wound complications that occur with similar or greater frequency with other incontinence surgeries. These overlapping risks across the incontinence surgeries (albeit lower with TVT, eg, voiding dysfunction, prolapse, chronic pelvic pain and dyspareunia) have long been reported in the medical literature and taught to pelvic surgeons [Chaliha C, Stanton SL. Complications of surgery for genuine stress incontinence. Br J Obstet Gynaecol. 1999 Dec;106(12):1238-45; Stanton SL. Stress incontinence: why and how operations work. Clin Obstet Gynaecol. 1985 Jun;12(2):369-77; Galloway NT, Davies N, Stephenson TP. The complications of colposuspension. Br J Urol. 1987 Aug;60(2):122-4; Jarvis GJ. Surgery for genuine stress incontinence. Br J Obstet Gynaecol. 1994 May;101(5):371-4; Francis WJ, Jeffcoate TN. Dyspareunia following vaginal operations. J Obstet Gynaecol Br Commonw. 1961 Feb;68:1-10; Haase P, Skibsted L. Influence of operations for stress incontinence and/or genital descensus on sexual life. Acta Obstet Gynecol Scand. 1988;67(7):659-61; Alcalay M, Monga A, Stanton SL. Burch colposuspension: a 10-20 year follow up. Br J Obstet Gynaecol. 1995 Sep;102(9):740-5; Demirci F, Yucel O, Eren S, Alkan A, Demirci E, Yildirim U. Long-term results of Burch colposuspension. Gynecol Obstet Invest. 2001;51(4):243-7; Weber AM, Walters MD, Piedmonte MR. Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol. 2000 Jun;182(6):1610-5], and are even the subject of more recent metaanalyses [Schimpf MO, Rahn DD, Wheeler TL, Patel M, White AB, Orejuela FJ, El-Nashar SA, Margulies RU, Gleason JL, Aschkenazi SO, Mamik MM, Ward RM, Balk EM, Sung VW; Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014 Jul;211(1):71.e1-71.e27; Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006375; Dmochowski RR, Blaivas JM, Gormley EA, Juma S, Karram MM, Lightner DJ, Luber KM, Rovner ES, Staskin DR, Winters JC, Appell RA; Female Stress Urinary Incontinence Update Panel of the American Urological Association Education and

Research, Inc., Whetter LE. Update of AUA guideline on the surgical management of female stress urinary incontinence. J Urol. 2010 May;183(5):1906-14].

Moreover, the Professional education videos, slide presentations and materials such as the 2001 TVT Surgeons Resource Monograph supplements the information presented, focusing on patient selection, use and operation of the device, risks and complication management. Topics covered in the Monograph include discussion and management of vaginal bleeding, retropubic hematoma, vascular injuries, bladder, bowel and vaginal perforations, difficulty placing needle, urethral injury and urethral erosion, infection, mesh extrusion, wound healing, voiding dysfunction, de novo urgency and urge incontinence, and urinary tract infection. When considering the basic knowledge of the intended reader, a trained pelvic surgeon, the IFU warns of risks specific to the device, it and the Professional education materials are informative and sufficient for the intended user, and the proffered risks outlined by Plaintiffs' experts are not necessary.

XIII. Summary

In conclusion, the TVT mid-urethral sling is the most studied incontinence device and procedure in our field, with well over 100 randomized controlled trials reporting on its outcomes. Individual studies have followed patients for up to 17 years following their TVT procedure and have shown that the device is safe, effective, and durable. Based on this extensive collection of short- and long-term data, the professional pelvic reconstructive surgery community worldwide has adopted the TVT as a first-line gold standard surgical treatment of stress urinary incontinence. The TVT has been endorsed in formal position statements and best practice guidelines by a large number of academic and clinical societies, including the American Urogynecologic Society (AUGS), American Urological Association (AUA), American College of Obstetricians and Gynecologists (ACOG), Society of Gynecologic Surgeons (SGS), the Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU), the

American Association of Gynecological Laparoscopists (AAGL), the International Urogynecologic Association (IUGA), the International Continence Society (ICS), and the National Institute of Health and Care Excellence (NICE) as a safe, durable, suitable procedure that has a low risk of complications and is associated with far less morbidity and higher or equal success to any operation previously described for treating stress urinary incontinence. Without the TVT, the treatment of stress urinary incontinence in women would suffer a tremendous setback and women's quality of life would suffer.

Olga Ramm, M.D.

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